

ORGANIC SYNTHESSES

AN ANNUAL PUBLICATION OF SATISFACTORY
METHODS FOR THE PREPARATION
OF ORGANIC CHEMICALS

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VOL. XVIII

NEW YORK
JOHN WILEY & SONS, INC.
LONDON: CHAPMAN & HALL, LIMITED

1938

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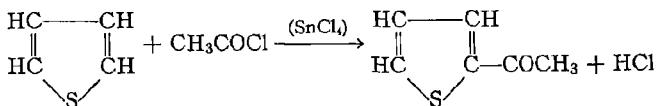
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ORGANIC SYNTHESSES

I

2-ACETOTHIENONE (Methyl 2-Thienyl Ketone)



Submitted by JOHN R. JOHNSON and G. E. MAY.

Checked by REYNOLD C. FUSON and E. A. CLEVELAND.

1. Procedure

In a 500-cc. round-bottomed, three-necked flask provided with a thermometer, dropping funnel, a liquid-sealed stirrer, and calcium chloride tube are placed 16.8 g. (0.2 mole) of thiophene (Org. Syn. 12, 72), 15.6 g. (0.2 mole) of acetyl chloride, and 200 cc. of dry benzene. The solution is cooled to 0°, and 52 g. (23 cc., 0.2 mole) of freshly distilled stannic chloride is added dropwise, with efficient stirring, during the course of about forty minutes. The reaction mixture assumes a purple color when the first drops of stannic chloride are added, and soon a purple solid precipitates.

After all the stannic chloride has been added, the cooling bath is removed and the mixture stirred for one hour longer. The addition product is hydrolyzed by the slow addition of a mixture of 90 cc. of water and 10 cc. of concentrated hydrochloric acid. The yellow benzene layer is separated, washed with 25 cc. of water, and dried over 5-10 g. of anhydrous calcium chloride. Benzene and unchanged thiophene (Note 1) are distilled through a short fractionating column (using an oil

bath), and the residual liquid is distilled under reduced pressure. The yield of 2-acetothienone, b. p. 89–91°/9 mm., is 20–21 g. (79–83 per cent of the theoretical amount) (Note 2).

2. Notes

1. By shaking the recovered benzene-thiophene mixture with a solution of 5.5 g. of mercuric chloride, 10 g. of sodium acetate, and 10 cc. of alcohol in 80 cc. of water, the unchanged thiophene is converted to the 2-chloromercurithiophene (containing a small amount of the dimercurichloride); from this the free thiophene can be obtained by treatment with hydrochloric acid. The recovered thiophene amounts to 2–2.5 g.

2. 2-Acetothienone has the following physical constants: d_4^{20} 1.168, n_D^{20} 1.566. Its semicarbazone melts at 186–187° (corr.).

3. Methods of Preparation

2-Acetothienone has been prepared by treating thiophene with acetyl chloride in the presence of aluminum chloride¹ or stannic chloride,² and by treating 2-chloromercurithiophene with acetyl chloride.³ The present method is essentially that of Stadnikoff and Goldfarb.² Stannic chloride is superior to aluminum chloride as a catalyst for this reaction as the latter induces polymerization of the thiophene.

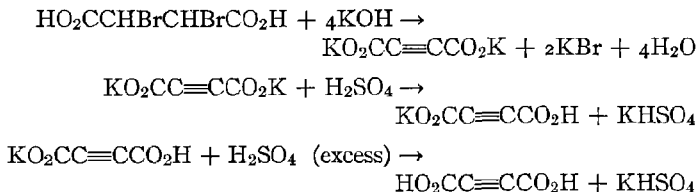
¹ Peter, Ber. **17**, 2643 (1884); Biedermann, *ibid.* **19**, 636 (1886).

² Stadnikoff and Goldfarb, *ibid.* **61**, 2341 (1928).

³ Volhard, Ann. **267**, 178 (1892); Steinkopf and Baumeister, *ibid.* **403**, 50 (1914).

II

ACETYLENEDICARBOXYLIC ACID



Submitted by T. W. ABBOTT, RICHARD T. ARNOLD, and RALPH B. THOMPSON.
Checked by REYNOLD C. FUSON and W. E. HOLLAND.

1. Procedure

A SOLUTION of potassium hydroxide is prepared by dissolving 122 g. (2.2 moles; 1.5 times the theoretical amount) of potassium hydroxide in 700 cc. of 95 per cent methyl alcohol (Note 1) contained in a 2-l. round-bottomed flask provided with a reflux condenser. To this alkaline solution is added 100 g. (0.36 mole) of α , β -dibromosuccinic acid (p. 17), and the mixture is refluxed for one hour and fifteen minutes on a steam bath. The reaction mixture is cooled and filtered with suction. The mixed salts are washed with 200 cc. of methyl alcohol (Note 2), and dried by pressing between filter papers; when dry the product weighs 144-150 g.

This salt mixture is dissolved in 270 cc. of water, and the acid potassium salt precipitated by adding 8 cc. of concentrated sulfuric acid in 30 cc. of water. After standing for three hours, or overnight, the mixture is filtered with suction (Note 3). The acid salt is then dissolved in 240 cc. of water to which 60 cc. of concentrated sulfuric acid has been added, and the solution extracted with five 100-cc. portions of ether. The combined ether solutions are evaporated to dryness on a steam bath,

leaving pure hydrated crystals of acetylenedicarboxylic acid. After drying for two days over concentrated sulfuric acid in a vacuum desiccator, the crystals decompose sharply at 175–176°. The yield is 30–36 g. (73–88 per cent of the theoretical amount).

2. Notes

1. The yield is slightly lower when 95 per cent ethyl alcohol is used.
2. This salt mixture is composed of potassium bromide and potassium acetylenedicarboxylate.
3. This acid salt is practically bromine-free and does not require additional washing.

3. Method of Preparation

The procedure described is essentially that of Bandrowski¹ and Baeyer² as modified by Ruggli.³ The same general method has also been used by Backer and van der Zanden,⁴ and by Moureu and Bongrand.⁵

¹ Bandrowski, *Ber.* 10, 838 (1877); see also Michael, *J. prakt. Chem.* (2) **52**, 295 (1895).

² Baeyer, *Ber.* 18, 677 (1885).

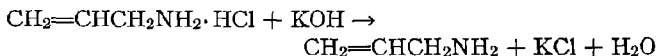
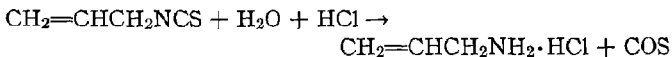
³ Ruggli, *Helv. Chim. Acta* **3**, 559 (1920).

⁴ Backer and van der Zanden, *Rec. trav. chim.* **47**, 776 (1928).

⁵ Moureu and Bongrand, *Ann. chim.* (9) **14**, 9 (1920).

III

ALLYLAMINE



Submitted by M. T. LEFFLER.

Checked by W. W. HARTMAN and E. J. RAHRS.

1. Procedure

In a 5-l. round-bottomed flask, equipped with a reflux condenser connected to a gas trap (Note 1), are placed 2 l. (12.1 moles) of 20 per cent hydrochloric acid and 500 g. (5.05 moles) of allyl isothiocyanate (Note 2). The mixture is refluxed over a free flame until the upper layer of allyl isothiocyanate has completely disappeared, about fifteen hours being required for the hydrolysis. When the reaction is complete, the solution is poured into a 3-l. beaker and concentrated on the steam bath until crystals begin to form in the hot solution. This occurs when the volume is approximately 400 cc. (Note 3).

The warm residue is then diluted with water to a volume of 500-550 cc. and placed in a 2-l. three-necked, round-bottomed flask equipped with a 500-cc. dropping funnel, a mercury-sealed mechanical stirrer, and a condenser arranged for distillation. The lower end of the condenser is fitted to a receiver consisting of a 500-cc. suction flask, whose side arm is connected to a reflux condenser (Note 4). The receiver is placed in an ice-salt bath and the three-necked flask in a water bath. The temperature of the water bath is raised to 95-98°, the stirrer is started, and a

solution of 400 g. (7.15 moles) of potassium hydroxide in 250 cc. of water is added dropwise from the funnel. As soon as the free hydrochloric acid is neutralized, the amine begins to distil. The rate of the addition of the alkali is regulated so as to maintain a dropwise distillation of allylamine, and, after the addition is complete, the heating and stirring are continued until all the amine has distilled.

The distillate is then dried over solid potassium hydroxide for twenty-four hours and finally over metallic sodium (Note 5). The allylamine is distilled from a water bath held at 70–78°, through a 12-in. fractionating column, and into a receiver immersed in an ice bath, the following fractions being collected: up to 54°/746 mm., and 54–57°/746 mm. The lower fraction amounts to 14–16 g., and on redistillation yields 6–8 g. of pure material. The total yield of pure allylamine boiling at 54–57°/746 mm. is 200–210 g. (70–73 per cent of the theoretical amount).

2. Notes

1. It is desirable to use a gas trap in order to prevent vapors of allyl isothiocyanate from escaping into the room. The gas trap described in Org. Syn. Coll. Vol. 1, 91, is suitable.

2. Eastman's "practical" grade (b. p. 150–152°) of allyl isothiocyanate was used in this preparation.

3. The rate of evaporation is greatly accelerated by allowing a stream of air to blow across the surface of the hot liquid. It is advantageous for the evaporation to proceed as far as possible in order to remove most of the free hydrochloric acid, and no harm is done if it continues until the solution turns to a semi-solid mass of crystals.

4. Care must be taken throughout to prevent loss of the product by volatilization. Furthermore, the vapors should not be allowed to come into contact with the nasal passages, as violent sneezing is produced.

5. The distillate should be kept cold (5–10°) during the drying process and should be separated from the potassium hydroxide before drying with sodium.

3. Methods of Preparation

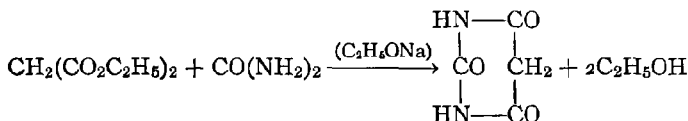
Allylamine has been prepared from allyl isothiocyanate by hydrolysis with dilute sulfuric ¹ or hydrochloric ² acid.

¹ Hofmann, Ber. **1**, 169 (1868).

² Gabriel and Eschenbach, Ber. **30**, 1124 (1897).

IV

BARBITURIC ACID



Submitted by J. B. DICKEY and A. R. GRAY.

Checked by REYNOLD C. FUSON and W. E. ROSS.

1. Procedure

In a 2-l. round-bottomed flask fitted with a reflux condenser protected by a calcium chloride tube 11.5 g. (0.5 gram atom) of finely cut sodium is dissolved in 250 cc. of absolute alcohol. To this solution is added 80 g. (0.50 mole) of ethyl malonate followed by 30 g. (0.50 mole) of dry urea dissolved in 250 cc. of hot (70°) absolute alcohol. After being well shaken the mixture is refluxed for seven hours on an oil bath heated to 110°. A white solid separates rapidly. After the reaction is completed, 500 cc. of hot (50°) water is added and then enough hydrochloric acid (sp. gr. 1.18) to make the solution acidic (about 45 cc.). The resulting clear solution is filtered and cooled in an ice bath overnight. The white product is collected on a Buchner funnel, washed with 50 cc. of cold water, and then dried in an oven at 105-110° for three to four hours. The yield of barbituric acid is 46-50 g. (72-78 per cent of the theoretical amount).

2. Methods of Preparation

Barbituric acid has been prepared by the action of phosphorus oxychloride on malonic acid and urea,¹ by treating an acetic acid solution of urea and malonic acid with acetic anhy-

dride,² and by the method of Michael³ from ethyl malonate and urea using sodium ethylate as a condensing agent.

The preparation described is an adaptation of that of Michael.

¹ Grimaux, *Compt. rend.* **87**, 752 (1878); Conrad and Guthzeit, *Ber.* **14**, 1643 (1881); Grimaux, *Bull. soc. chim. (2)* **31**, 146 (1879); Matignon, *Ann. chim. phys. (6)* **28**, 289 (1893).

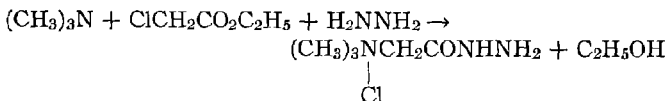
² Biltz and Wittek, *Ber.* **54**, 1035 (1921).

³ Michael, *J. prakt. Chem. (2)* **35**, 449 (1887); Tafel and Weinschenk, *Ber.* **33**, 3383 (1900); Gabriel and Colman, *Ber.* **37**, 3657 (1904).

V

BETAINÉ HYDRAZIDE HYDROCHLORIDE

(Girard's Reagent)



Submitted by ANDRÉ GIRARD.

Checked by L. F. FIESER and ROBERT P. JACOBSEN.

1. Procedure

In a 1-l. three-necked flask fitted with a stirrer, a thermometer, and an ice-cooled spiral condenser (Org. Syn. Coll. Vol. **1**, 515) is placed a solution of 98 g. (0.80 mole) of ethyl chloroacetate in 200 cc. of absolute alcohol. The solution is cooled to 0° by stirring in a salt-ice bath, and, after the stirrer is stopped, 74 cc. (49 g., 0.83 mole) of trimethylamine, measured after precooling to -5°, is added all at once. The exothermic reaction is controlled sufficiently by cooling so that the temperature of the mixture rises to 60° in the course of about one hour (Note 1). When there is no longer any heat effect, the mixture is allowed to stand at room temperature for twenty hours (without replenishment of the condenser ice).

The condenser is removed, the thermometer replaced by a dropping funnel, and 40 g. (0.80 mole) of 100 per cent hydrazine hydrate (Note 2) added, with stirring, in the course of ten to fifteen minutes. After being stirred for forty-five minutes longer, the solution is cooled slightly, and, unless crystallization of the reaction product starts spontaneously, the walls of the vessel are scratched with a glass rod to induce crystallization (Note 3). The product separates in fine, colorless needles. After being thoroughly cooled in an ice bath, the highly hygro-

scopic salt is collected quickly on a Buchner funnel, washed with 150 cc. of cold absolute alcohol, and pressed dry under a rubber dam. Dried in a vacuum desiccator over concentrated sulfuric acid, this material weighs 100-108 g. A further crop can be obtained after distilling 200-300 cc. of solvent from the mother liquor and washings at the pressure of the water pump. The total yield of salt, m. p. 175-180°, with decomposition, is 112-120 g. (83.5-89.5 per cent of the theoretical amount) (Notes 4, 5, and 6).

2. Notes

1. Without external cooling the temperature rises to about 75° and it is difficult to avoid some loss of amine.

2. The product supplied by Fraenkel and Landau, Germany, is satisfactory.

The 42 per cent hydrazine hydrate solution supplied by the Eastman Kodak Company is too dilute for use as such, but may be concentrated by distillation with xylene.¹ A mixture of 144 cc. (150 g.) of the 42 per cent solution and 230 cc. of xylene is distilled from a 500-cc. flask through a 17-cm. Hempel column fitted into a cork covered with tin foil. After distillation of the xylene, with about 85 cc. of water, the residue yields on distillation 45-50 g. of 80-85 per cent hydrazine hydrate. This material, assayed best by titration with standard acid using methyl orange as indicator, may be used as such or concentrated further (see Note 6).

3. When more dilute hydrazine hydrate is used, the crystallization is slower, but it is not advisable to cool the solution thoroughly until crystals have begun to appear.

4. Although this material contains a small amount of the symmetrical dihydrazide, which is not easily eliminated on crystallization, it is entirely satisfactory for use as a reagent for the isolation of ketones. A purer product, m. p. 192°, with decomposition, can be obtained by adding the solution prepared from ethyl chloroacetate and trimethylamine to an alcoholic solution containing a considerable excess of the hydrazine hydrate.

5. When stored in a dry, tightly stoppered container the reagent can be kept for long periods without deteriorating (odor), but samples withdrawn after some time are best recrystallized from absolute alcohol before use.

6. The yields obtained by the checkers when using 75 per cent and 50 per cent hydrazine hydrate were 78 per cent and 66 per cent, respectively, of the theoretical amount.

3. Method of Preparation

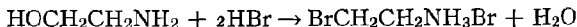
The above procedure is essentially that of Girard and Sandulesco.²

¹ Hurd and Bennett, *J. Am. Chem. Soc.* **51**, 265 (1929).

² Girard and Sandulesco, *Helv. Chim. Acta* **19**, 1095 (1936).

VI

β -BROMOETHYLAMINE HYDROBROMIDE



Submitted by FRANK CORTESE.

Checked by C. S. MARVEL and C. L. FLEMING.

1. Procedure

ONE KILOGRAM (16 moles) of ice-cold ethanolamine (Note 1) is added, through a dropping funnel, with mechanical stirring, to 7 l. (9.94 kg., 52 moles) of ice-cold hydrobromic acid (sp. gr. 1.42) (Note 2) contained in a 12-l. round-bottomed flask. The flask is attached to an efficient fractionating column and heated until 1850 cc. of distillate has been collected. The rate of heating is then diminished to a point at which the liquid ceases to distil and merely refluxes. The heating under reflux is continued for one hour. At the end of this time, 700 cc. more is distilled, and the solution is again heated under reflux for one hour. This procedure is followed with 600-, 300-, 250-, 150-, 100- and 50-cc. portions of distillate. The process may be interrupted at any time. The solution is finally heated under reflux for three hours, and 2300 cc. of crude hydrobromic acid distilled. The total volume of distillate, including that which is collected during refluxing, must not be less than 6270 cc., nor more than 6330 cc.

The dark-colored residue is divided into two approximately equal portions, and each is poured, while still hot, into a 4-l. beaker. After the liquid has cooled to about 70°, 1650 cc. of acetone is added to each portion. The mixture is stirred well, so that as much as possible of the dark-colored solid is brought into contact with the acetone. After standing in the ice box overnight, the β -bromoethylamine hydrobromide is collected on a filter, washed with acetone until colorless (Note 3), and air-dried

for about fifteen minutes. The filtrates are combined, concentrated to a volume of 1 l., and cooled. After seeding, a second crop of nearly pure material is obtained. By evaporation to a syrup, cooling, and seeding, a third crop (slightly colored) is obtained. All three crops are suitable for the taurine synthesis. The yield is about 2800 g. (83 per cent of the theoretical amount).

2. Notes

1. Commercial ethanolamine is fractionated in a glass apparatus, and the fraction boiling at 167–169° is used.

2. The hydrobromic acid must have a specific gravity of at least 1.42.

3. It may be advisable for effective washing to transfer the crude cake to a mortar and crush it.

3. Methods of Preparation

β -Bromoethylamine hydrobromide has been prepared by the reaction of potassium phthalimide with ethylene bromide, followed by hydrolysis,¹ by the addition of hydrogen bromide to ethyleneimine,² and by the present method.³

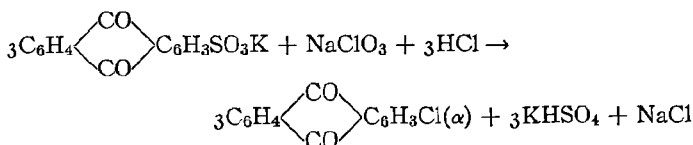
¹ Gabriel, Ber. **21**, 566 (1888).

² Gabriel, *ibid.* **21**, 1049 (1888); Gabriel and Stelzner, *ibid.* **28**, 2929 (1895).

³ Gabriel, *ibid.* **50**, 826 (1917); Cortese, J. Am. Chem. Soc. **58**, 191 (1936).

VII

α -CHLOROANTHRAQUINONE



Submitted by W. J. SCOTT and C. F. H. ALLEN.
 Checked by L. F. FIESER and E. B. HERSHBERG.

1. Procedure

A 2-l. three-necked flask fitted with a stirrer (Notes 1 and 2), condenser, and dropping funnel (Note 3) is mounted in the hood, and in it are placed 20 g. (0.061 mole) of potassium anthraquinone- α -sulfonate (p. 72), 500 cc. of water, and 85 cc. (1 mole) of concentrated hydrochloric acid. The solution is heated to boiling and stirred, while a solution of 20 g. (0.19 mole) of sodium chlorate (Note 4) in 100 cc. of water is added dropwise over a period of three hours (Note 5). The mixture is refluxed very slowly for an additional hour before the precipitated α -chloroanthraquinone is collected by suction filtration and washed free from acid with hot water (about 350 cc.). After drying *in vacuo* at 100°, the bright yellow product melts at 158–160° (corr.) and weighs 14.6–14.7 g. (97–98 per cent of the theoretical amount) (Notes 6 and 7).

2. Notes

1. Since the mixture tends to foam toward the end of the reaction, it is advisable to use an effective stirrer. A Hershberg stirrer (Org. Syn. 17, 31) of tantalum wire gave good service in the hands of the checkers, and the metal was not appreciably attacked after repeated use.

2. Although a glass sleeve for the stirrer is fairly satisfactory, it is better to use a seal of the conventional type (Org. Syn. Coll. Vol. 1, 31, Fig. 2a) filled with water rather than mercury.

3. Since the usual dropping funnel has the disadvantage of requiring considerable attention from the operator, the checkers found it much more convenient to employ the device (of E. B. H.) shown in Fig. 1.

4. Potassium chlorate is less satisfactory because of its lower solubility.

5. If the addition is too rapid, or the boiling too vigorous, chlorinating gases are lost through the condenser.

6. Crystallization of the product from 200 cc. of *n*-butyl alcohol gives 13.4 g. of material in the form of yellow needles, m. p. 161–162° (corr.). Larger amounts are conveniently crystallized from toluene, using 2 cc. per gram.

7. The melting point given for highly purified α -chloroanthraquinone is 162.5° (corr.). The possible contaminants include the β -isomer, 1,5-, and 1,8-dichloroanthraquinone, all of which melt at higher tem-

peratures but depress the melting point of the α -monochloro compound.

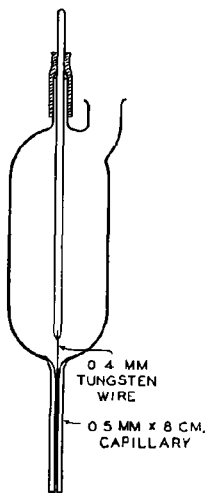


FIG. 1

3. Methods of Preparation

α -Chloroanthraquinone has been prepared from α -aminoanthraquinone by the diazo reaction,¹ by the action of thionyl chloride on potassium anthraquinone- α -sulfonate under pressure,² and by the above process.³

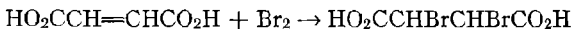
¹ Groggins, "Unit Processes in Organic Synthesis," p. 175, McGraw-Hill Book Company, New York, 1935.

² Ger. pat. 267,544 [Chem. Zentr. I, 89 (1914)].

³ Ger. pat. 205,195 [Chem. Zentr. I, 414 (1909)]; Ger. pat. 228,876 [Chem. Zentr. I, 102 (1911)]; Ullmann and Ochsner, Ann. 381, 1 (1911).

VIII

α,β -DIBROMOSUCCINIC ACID



Submitted by HERBERT S. RHINESMITH.

Checked by REYNOLD C. FUSON and W. E. ROSS

1. Procedure

IN a 2-l. three-necked, round-bottomed flask equipped with a mechanical stirrer (Note 1), dropping funnel, and Friedrichs condenser¹ (Note 2), are placed 200 g. (1.72 moles) of fumaric acid (Org. Syn. 11, 46) (Note 3) and 400 g. of water (Note 4). The materials are thoroughly mixed until the fumaric acid has been completely wet by the water. The resulting thick, viscous mass is then stirred vigorously (Note 5) and brought to boiling by heating on a wire gauze with a Bunsen flame (Note 6).

Two hundred and seventy-six grams (94.3 cc., 1.72 moles) of bromine (Note 7) is now added as rapidly as possible through the dropping funnel, the rate of addition being so controlled that the Friedrichs condenser is continuously about half full of the refluxing liquid (Note 8). This operation takes about one hour (Note 9). After about 100 g. of bromine has been added, the dibromosuccinic acid forms rapidly and separates in tiny white needles. At the completion of the reaction there should be a slight excess of bromine, as indicated by the red color of the solution. Occasionally 5-10 g. of bromine has to be added at this point to insure an excess.

The reaction flask is now surrounded with ice water and cooled to 10°, with stirring. The product is then collected on a large Buchner funnel, and washed with cold water to remove the bromine liquor. The ~~filtrate may~~ ^{filtrate} be discarded, as it contains only impurities. The ~~material is dried~~ ^{material} is dried overnight at room tem-

perature and need not be recrystallized; the yield is 343–400 g. (72–84 per cent of the theoretical amount).

2. Notes

1. A heavy stirrer with as large a paddle as possible is used, in order to rotate the mass of crystals formed during the course of the reaction. A mercury seal is unnecessary, but it is advisable to have the stirrer bearing extend beneath the surface of the liquid.

2. Glass connections or rubber stoppers should be used throughout, as corks are rapidly disintegrated by the hot bromine.

3. Commercial fumaric acid ("practical") is sufficiently pure for this preparation.

4. Any larger amount of water leads to the formation of monobromomalic acid, tartaric acid, and compounds of unknown composition.²

5. Vigorous stirring is essential to obtain good yields.

6. It is necessary to keep the reaction mixture boiling throughout the entire course of the reaction. During the addition of the bromine, however, the size of the flame should be reduced considerably, because the reaction is exothermic.

7. The apparatus should be set up under a hood, or the top of the condenser connected to a gas absorption trap for the removal of bromine vapor, a small amount of which escapes continually under the conditions of the experiment.

8. By this procedure most of the unchanged bromine is washed back into the flask, so that the amount escaping from the top of the condenser is kept at a minimum.

9. If the bromine is added over a much longer period of time, the yield is materially decreased.

3. Methods of Preparation

α,β -Dibromosuccinic acid may be prepared by heating succinic acid with bromine and water in a closed tube at 180°;³ by heating succinic acid, red phosphorus, and bromine in a closed tube at 140°;⁴ by heating fumaric acid with 2 moles of bromine in acetic

acid for seven hours in a sealed tube at 100° ;⁵ from fumaric acid, bromine, and water at 100° under pressure;⁶ and by the method described above.

¹ Friedrichs, Z. angew. Chem. **33**, I, 30 (1920).

² Kekulé, Ann. Spl. Bd. **1**, 338 (1861).

³ Kekulé, Ann. **117**, 120 (1861); Ann. Spl. Bd. **1**, 338 (1861); Bourgoin, Bull. soc. chim. (2) **19**, 148 (1873); Wilson and Wenzke, J. Am. Chem. Soc. **57**, 1265 (1935).

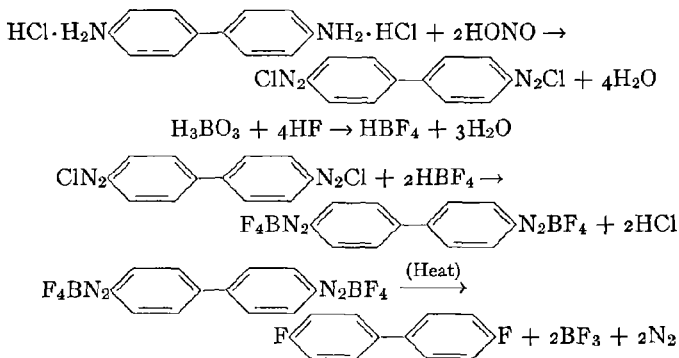
⁴ Gorodetzky and Hell, Ber. **21**, 1729 (1888).

⁵ Michael, J. prakt. Chem. (2) **52**, 289 (1895).

⁶ Kekulé, Ann. Spl. Bd. **1**, 129 (1861); Bacyer, Ber. **18**, 674 (1885).

IX

4,4'-DIFLUOROBIPHENYL



Submitted by G. SCHIEMANN and W. WINKELMÜLLER.

Checked by W. W. HARTMAN, J. R. BYERS, and J. B. DICKEY.

1. Procedure

A MIXTURE of 280 g. (1.52 moles) of commercial benzidine and 880 cc. (10.23 moles) of concentrated hydrochloric acid (sp. gr. 1.182) is placed in a 5-l. round-bottomed flask and warmed on a steam bath for one to two hours, with occasional shaking, to form the dihydrochloride. The flask is then equipped with a mechanical stirrer and a dropping funnel, and cooled, with stirring, to -10° in an ice-salt bath. When this temperature has been reached, the benzidine dihydrochloride is tetrazotized over a period of two hours with a solution of 232 g. (3.19 moles) of 95 per cent sodium nitrite in 800 cc. of water, until a faint test for nitrous acid with starch-iodide paper is obtained after twenty minutes. During this reaction, the temperature is kept below -5° .

Concurrently with the tetrazotization, 104 g. (1.68 moles) of boric acid is dissolved in 222 g. (6.66 moles) of 60 per cent hydrofluoric acid (Note 1). The solution is made in a 1-l. beaker, which has been coated inside with paraffin, and is cooled in an ice bath. The boric acid is added slowly in small portions, and the mixture is stirred with a lead rod. It is necessary to keep the temperature below 20–25° in order that the heat of solution may not melt the paraffin from the walls of the beaker (Note 2).

The ice-cold fluoboric acid solution is added rather rapidly, with stirring, to the finished tetrazo solution, the temperature being kept below 10°. A thick paste of 4,4'-biphenylene-bis-diazonium borofluoride forms. The mixture is stirred at 10° for twenty to thirty minutes. It is then collected on a 19-cm. Buchner funnel, and washed consecutively with about 200 cc. of cold water, 200 cc. of cold commercial methyl alcohol, and 200 cc. of commercial ether; the cake is sucked as dry as possible between washings. It is then dried in a vacuum desiccator over concentrated sulfuric acid (sp. gr. 1.84). The yield of the dry solid is 393–400 g. (68–69 per cent of the theoretical amount). The product decomposes at 135–137°.

A 1-l. distilling flask with a wide side arm may be used for the decomposition of the tetrazonium borofluoride. A 500-cc. distilling flask is fastened directly to the side arm of the decomposition flask and cooled with running water. To the side arm of the receiver is connected a rubber tube which is placed over 2 l. of water in a 5-l. flask (Note 3). The solid to be decomposed (Note 4) is placed in the decomposition flask and heated at the upper edge with a Bunsen burner. When white fumes begin to be evolved, the burner is removed and the decomposition permitted to continue spontaneously. More heat is applied as needed. Finally vigorous heating is employed to insure complete decomposition. Some 4,4'-difluorobiphenyl is collected in the receiver, but the larger portion remains in the decomposition flask, from which it is recovered by steam-distilling the black residue. A second steam distillation gives a pure white compound melting at 88–89°, after drying in an oven at 60–70°.

When 153 g. of the tetrazonium borofluoride is decomposed in this manner, 61-62 g. of 4,4'-difluorobiphenyl is obtained (80-81.5 per cent of the theoretical amount, based on the tetrazonium borofluoride; 54-56 per cent based on the benzidine used).

2. Notes

1. Fluoboric acid is now a commercial product. For this size preparation, 355.5 g. of the commercial 40 per cent fluoboric acid is required.

2. A small lead jar is excellent for preparing the solution. By the use of a lead stirrer of the usual shape, mechanical stirring may be used. The stirrer should be thrust through a hole in a lead cover of sufficient size to prevent splashing of the hydrofluoric acid.

3. A convenient apparatus is made by connecting a 1-l. round-bottomed flask by means of a bent tube of large diameter (2 cm.) to a second 1-l. round-bottomed flask containing 500 cc. of water. The second flask is equipped with an exit tube, and the gases which do not dissolve in the water are led into a hood.

4. It is very necessary that the tetrazonium borofluoride be dried completely. If the solid is wet, the decomposition proceeds very vigorously. There is formed at the same time a product of higher melting point (160°) as well as some tar. These products, although not volatile with steam, lower the yield of the 4,4'-difluorobiphenyl very materially.

3. Methods of Preparation

4,4'-Difluorobiphenyl has been prepared from 4,4'-biphenyl-bis-diazonium piperidide (by diazotizing benzidine and coupling with piperidine) and concentrated hydrofluoric acid;¹ by the action of sodium on *p*-fluorobromobenzene in ether;² from benzidine by tetrazotization and decomposing the biphenyl-bis-diazonium salt with concentrated hydrofluoric acid;³ by the above method in the presence of ferric chloride;⁴ and by the prolonged contact of the vapors of fluorobenzene with a red-hot wire.⁵ The method described here is the most satisfactory for

use in the laboratory and is an improvement on the method of Balz and Schiemann.⁶

¹ Wallach, Ann. **235**, 271 (1886).

² Wallach and Heusler, Ann. **243**, 244 (1888).

³ Valentiner and Schwarz, Ger. pat. 96,153 [Frdl. **5**, 910 (1897-1900)].

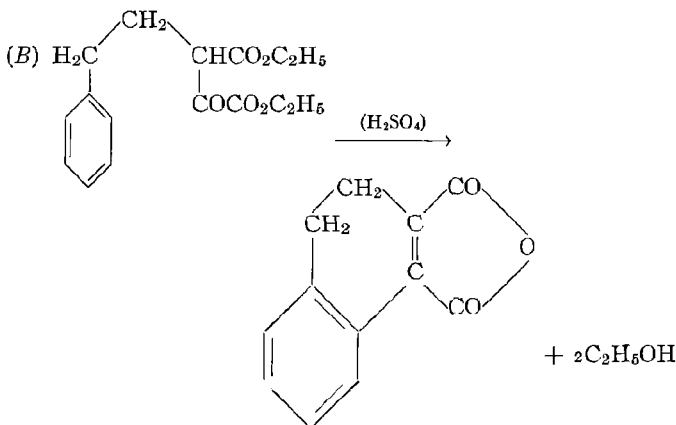
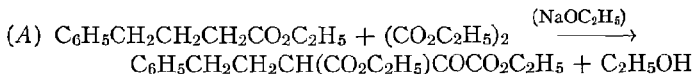
⁴ Valentiner and Schwarz, Ger. pat. 186,005 [Frdl. **8**, 1237 (1905-1907)].

⁵ Meyer and Hofmann, Monatsh. **38**, 149 (1917).

⁶ Balz and Schiemann, Ber. **60**, 1189 (1927).

X

3,4-DIHYDRO-1,2-NAPHTHALIC ANHYDRIDE



Submitted by E. B. HERSHBERG and L. F. FIESER.
Checked by C. R. NOLLER and S. KINSMAN.

1. Procedure

(A) *Ester Condensation*.—In a 1-l. round-bottomed flask fitted with a reflux condenser equipped with a dropping funnel and a calcium chloride tube is placed a suspension of 6.1 g. (0.27 mole) of powdered sodium (Note 1) in 150 cc. of absolute ether. A solution of 12.6 g. (0.27 mole) of absolute ethyl alcohol (Note 2) and 50 cc. of absolute ether is added, and the mixture allowed to stand overnight to complete the reaction. To the suspension of sodium ethylate, 57 g. (0.39 mole) of ethyl oxalate (Org. Syn. Coll. Vol. 1, 256), diluted with 50 cc. of ether, is added in portions. After the spontaneous reaction subsides, the pale

yellow solution is allowed to stand for one-half hour, and 50 g. (0.26 mole) of ethyl γ -phenylbutyrate (Note 3), diluted with 50 cc. of absolute ether, is added. The mixture is refluxed gently for twenty-four hours (Note 4).

The deep red solution is cooled in an ice bath and neutralized by the addition, with shaking, of an ice-cold solution of 15 cc. of concentrated sulfuric acid in 200 cc. of water. The ether layer is separated, washed with water, and dried over sodium sulfate. The ether is removed by dropping the solution from a separatory funnel the stem of which extends to the bottom of an evacuated Claisen flask heated on the steam bath. The residue is a pale yellow oil consisting of a mixture of ethyl α -ethoxalyl- γ -phenylbutyrate and unchanged ethyl oxalate (Note 5).

(B) *Cyclization*.—The above oil is poured slowly into 500 cc. of concentrated sulfuric acid, the temperature being kept at 20–25° by cooling in an ice bath. After standing for one and one-half hours at 20–25°, the deep red solution is poured on 3 l. of ice and water. The anhydride, precipitated as a pale yellow solid, is collected and washed thoroughly with water. Dried *in vacuo* at 25°, the material weighs 40–45 g. and melts at 117–122°. Distillation under diminished pressure gives a light yellow product, m. p. 122–124°. The yield is 38–42 g. (73–81 per cent of the theoretical amount). This material is suitable for most purposes. Crystallization from 100 cc. of benzene with the addition of 75 cc. of ligroin (b. p. 60–80°) gives 34–41 g. of pale yellow prisms, m. p. 125–126° (Note 6).

2. Notes

1. The powdered sodium for this preparation may be prepared as in *Org. Syn. Coll. Vol. 1*, 247, or according to the following procedure for potassium, using xylene instead of toluene. With certain other γ -arylbutyric esters it is better to use potassium. Commercial potassium is cleaned by melting it under toluene, and 10.4 g. (0.27 mole) of the metal and 150 cc. of dry toluene are placed in the 1-l. flask. After the liquid is heated to boiling on a hot plate, the flask is removed and closed with a ground-glass stopper carrying a sealed-on stopcock. Apparatus

with interchangeable ground joints is essential. After one shake with the stopcock open to relieve superheating, the stopcock is closed, and the flask is shaken quickly and vigorously to powder the metal. The mixture is allowed to cool undisturbed, and nitrogen is admitted. The stopper is replaced by a distilling head carrying a 500-cc. flask, into which the toluene can be decanted. The powdered metal is washed several times with absolute ether and finally covered with ether (150 cc.) and converted into the ethylate with 12.6 g. of alcohol diluted with 150 cc. of ether. Traces of potassium in the wash liquors are destroyed with safety by treatment under reflux with alcohol diluted with ether.

2. The alcohol was dried according to *Org. Syn. Coll. Vol. 1*, 246, Note 1.

3. Ethyl γ -phenylbutyrate is prepared in 85–88 per cent yields by refluxing for three hours a mixture of 50 g. of γ -phenylbutyric acid (*Org. Syn.* 15, 64), 150 cc. of alcohol dried over lime, and 5 g. of concentrated sulfuric acid. The ester is isolated by distilling 100 cc. of the alcohol under reduced pressure from a steam bath, diluting with 200 cc. of water, separating, and extracting the aqueous layer twice with 50-cc. portions of ether. The combined ester and ether layers are dried with sodium sulfate, the ether removed, and the residue distilled under diminished pressure; the portion boiling at 144–147° at 19 mm. is collected.

4. With potassium ethylate the reaction is complete in twelve hours.

5. The keto ester decomposes on distillation, even under diminished pressure.

6. For the cyclization of the keto esters from γ -naphthylbutyric esters it is advisable to use 80 per cent sulphuric acid, and to heat the mixture, with stirring, at 70–80° for one-half hour.

3. Method of Preparation

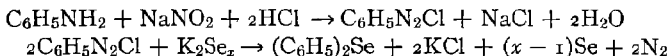
The above procedure is a modification ¹ of the method of von Auwers and Möller.²

¹ Fieser and Hershberg, *J. Am. Chem. Soc.* 57, 1851 (1935).

² von Auwers and Möller, *J. prakt. Chem.* 217, 137 (1925).

XI

DIPHENYL SELENIDE



Submitted by HENRY M. LEICESTER.

Checked by W. W. HARTMAN and R. H. BULLARD.

1. Procedure

IN a 500-cc. beaker are placed 360 g. (6.4 moles) of powdered potassium hydroxide and 240 g. (3 gram atoms) of black powdered selenium, which have been previously ground together in a mortar. This mixture is heated (Note 1) in an oil bath at 140-150° until a thick, dark red liquid is formed (Note 2), and then it is added (Note 3) in small portions to 400 cc. of ice water in a 5-l. flask. The solution is kept in an ice bath until used.

To 375 cc. (4.3 moles) of hydrochloric acid (sp. gr. 1.18) and 200 g. of ice is added 139.6 g. (1.5 moles) of aniline. The resulting solution is diazotized with a solution of 103.5 g. (1.5 moles) of c. p. sodium nitrite, ice being added to the reaction mixture, as necessary, in order to keep the temperature below 5°. The final volume of the diazotized solution is about 1 l. This solution is added in a slow stream from a dropping funnel to the potassium selenide solution, which is being vigorously stirred with a mechanical stirrer. When all the diazotized solution has been added, the red aqueous solution is decanted from the dark oil which forms and is heated to boiling (Note 4). It is then poured back on the oil, the mixture is well stirred (Note 5), 200 cc. of chloroform is added, and the selenium collected on a filter and washed with a little more chloroform (Note 6). After the chloroform layer is separated, the aqueous layer is again

extracted with 200 cc. of chloroform. The combined extracts are then distilled, the diphenyl selenide being collected from 300 to 315°. The yield of yellow oil of rather unpleasant odor is 138–150 g. (79–86 per cent of the theoretical amount) (Note 7). If a purer product is desired, this material can be distilled under diminished pressure. It boils at 165–167°/12 mm.

2. Notes

1. Although no toxic gases are evolved in this reaction, the mixture has a rather unpleasant odor, so that it is best to use a hood throughout.

2. If the potassium hydroxide and selenium are absolutely dry, a thick paste is formed. The addition of a few cubic centimeters of water will form the dark red liquid mentioned.

3. If the mass is allowed to cool and solidify, it becomes very hard and is difficult to break up and dissolve.

4. Unless the aqueous layer is heated separately, the beaker containing the viscous oil always cracks, no matter how well the liquid is stirred.

5. This treatment converts the selenium from the red, colloidal form into the more easily filterable black modification.

6. The amount of selenium recovered is 101–115 g.

7. When smaller amounts of the selenide are prepared, the yield drops to 70–75 per cent. The method may be applied equally well to the preparation of the selenides from the three toluidines, giving yields of 50–70 per cent.

3. Methods of Preparation

The method described here is a modification of that of Schoeller.¹ Diphenyl selenide has also been prepared from diazotized aniline and alkali monoselenides;² by the Friedel-Crafts reaction with benzene and selenium tetrachloride³ or selenium dioxide;⁴ from diphenyl sulfone and selenium;⁵ from phenylmagnesium bromide and selenium,⁶ selenium dichloride,⁷

selenium oxychloride,⁷ or selenium dibromide,⁸ and from sodium selenophenolate and bromobenzene.⁹

¹ Schoeller, Ber. **52**, 1517 (1919).

² Lesser and Weiss, *ibid.* **47**, 2510 (1914).

³ Krafft and Kaschau, *ibid.* **29**, 428 (1896).

⁴ Lyons and Bradt, *ibid.* **60**, 60 (1927).

⁵ Krafft and Vorster, *ibid.* **26**, 2813 (1893); Krafft and Lyons, *ibid.* **27**, 1761 (1894).

⁶ Taboury, Ann. chim. (8) **15**, 5 (1908).

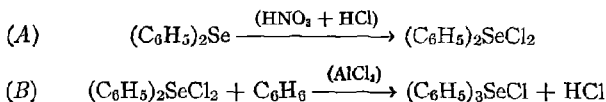
⁷ Strecker and Willing, Ber. **48**, 196 (1915).

⁸ Pieroni and Balduzzi, Gazz. chim. ital. **45**, II, 106 (1915).

⁹ Foster and Brown, J. Am. Chem. Soc. **50**, 1182 (1928).

XII

DIPHENYLSELENIUM DICHLORIDE AND TRIPHENYLSELENONIUM CHLORIDE



Submitted by HENRY M. LEICESTER.

Checked by W. W. HARTMAN and R. H. BULLARD.

1. Procedure

(A) *Diphenylselenium Dichloride*.—One hundred twenty-five grams (0.53 mole) of diphenyl selenide (p. 27) is added in portions to 250 cc. (4 moles) of nitric acid (sp. gr. 1.42) in a 1.5-l. beaker. Hydrochloric acid (sp. gr. 1.18) is then added until precipitation is complete. About 170 cc. (2 moles) of acid is required. The mixture is then diluted with 500 cc. of water, and the yellow precipitate is separated by filtration and air-dried. The crude product is purified by extracting with 500 cc. of boiling benzene. The crystals which separate on cooling are collected on a filter and the filtrate used for a further extraction. Three such treatments are necessary for a complete crystallization. The yield of yellow needles, decomposing at 187–188°, is 137–141 g. (85–87 per cent of the theoretical amount).

(B) *Triphenylselenonium Chloride*.—To 87 g. (100 cc., 1.12 moles) of benzene in a 1-l. three-necked flask provided with a mechanical stirrer, is added 30 g. (0.22 mole) of anhydrous aluminum chloride. The suspension is cooled in an ice bath, and to it is added, with stirring, 40 g. (0.13 mole) of diphenylselenium dichloride in portions of approximately 1 g. at a time over a period of twenty-five minutes. Before each addition the

temperature should be below 10° to prevent the final product from becoming dark. When the addition is complete, the reaction mixture is allowed to stand for three hours at room temperature, and then 200 cc. of water is added cautiously (Note 1). The benzene layer is separated and discarded. If the water layer is colored, further extractions with benzene will remove most of the color without reducing the yield. The water layer is then extracted three times with 50-cc. portions of chloroform. The combined extracts are concentrated to a volume of 40 cc. and treated with 120 cc. of ether (Note 2). A yellow oil precipitates and solidifies almost at once to a white powder. The triphenylselenonium chloride is collected on a filter and recrystallized from 300 cc. of methyl ethyl ketone to which 20 cc. of water has been added (Note 3). The yield of anhydrous product, after drying at 100° , is 30 g. (67 per cent of the theoretical amount) (Note 4).

2. Notes

1. Much heat is evolved during the first part of the hydrolysis.

2. Triphenylselenonium chloride may be precipitated from aqueous solution as the zinc chloride double salt.¹

3. Triphenylselenonium chloride is only slightly soluble in anhydrous methyl ethyl ketone (2 g. per 300 cc.). Using the water-methyl ethyl ketone mixture, the substance crystallizes with two molecules of water. This can be removed by heating for half an hour at 100° , but is again taken up from moist solvents or moist air.

4. This method can also be used for the preparation of *p*-tolyl- or of mixed phenyl-*p*-tolylselenonium salts.

3. Methods of Preparation

Diphenylselenium dichloride has been prepared from diphenyl selenide ^{2,3} by the action of chlorine and by treatment first with nitric acid and then hydrochloric acid. Triphenylselenonium chloride has been prepared by fusing together diphenylmercury

and diphenylselenium dichloride,⁴ and by the action of diphenylselenium dichloride on benzene in the presence of aluminum chloride.³

¹ Crowell and Bradt, J. Am. Chem. Soc. **55**, 1500 (1933).

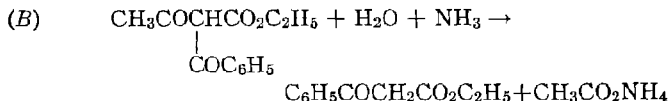
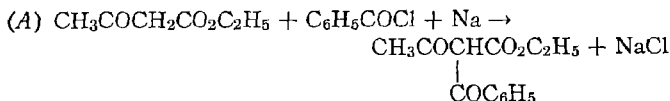
² Foster and Brown, *ibid.* **50**, 1182 (1928).

³ Leicester and Bergstrom, *ibid.* **51**, 3587 (1929).

⁴ Leicester and Bergstrom, *ibid.* **53**, 4428 (1931); Leicester, *ibid.* **57**, 1901 (1935).

XIII

ETHYL BENZOYLACETATE



Submitted by R. L. SHRINER, A. G. SCHMIDT, and L. J. ROLL.

Checked by C. R. NOLLER and I. BERGSTEINSON.

1. Procedure

(A) *Preparation of Ethyl Benzoylacetate*.—In a 5-l. three-necked flask, fitted with a liquid-sealed mechanical stirrer and reflux condenser, are placed 3.4 l. of dry benzene (Note 1), 195 g. (1.5 moles) of ethyl acetoacetate, and 34.5 g. (1.5 gram atoms) of clean sodium. The mixture is heated on a steam cone with stirring and allowed to reflux gently for twenty-four hours. After the suspension of the sodioacetoacetic ester has been cooled slightly, 263 g. (1.87 moles) of benzoyl chloride is added over a period of three hours. The mixture is refluxed with stirring for an additional eight hours. It is then cooled to room temperature, and 375 g. of cracked ice added. After shaking thoroughly, the benzene layer, which contains the ethyl benzoylacetate, is separated, washed with 75 cc. of 5 per cent sodium bicarbonate solution, dried with sodium sulfate, and the benzene distilled (Note 2). The residue is distilled *in vacuo* from a 500-cc. Claisen flask with a 50-cm. fractionating side arm. After a small fore-run of benzoyl chloride, the fraction boiling at 142–148°

at 6 mm., or $177-181^{\circ}$ at 20 mm., is collected. The yield is 223-263 g. (63-75 per cent of the theoretical amount).

(B) *Hydrolysis of Ethyl Benzoylacetate*.—Thirty-two grams (0.6 mole) of ammonium chloride is dissolved in 150 cc. (8.3 moles) of water, in a 500-cc. Erlenmeyer flask, and 10 cc. (0.15 mole) of ammonia (sp. gr. 0.9) added. After the solution is warmed to 42° , 58.5 g. (0.25 mole) of ethyl benzoylacetate at 20° is added quickly, and the mixture shaken (Note 3). The flask is placed in a water bath at 42° for exactly ten minutes and then cooled rapidly by placing it in an ice bath. The solution is extracted twice with 100-cc. portions of ether, and the ether solution dried with anhydrous magnesium sulfate. The ether is distilled, and the residue distilled *in vacuo*; the yield is 37.0-37.5 g. (77-78 per cent of the theoretical amount) of ethyl benzoylacetate boiling at $132-137^{\circ}$ at 4 mm., or $165-169^{\circ}$ at 20 mm.

2. Notes

1. The benzene was dried by distillation, the first portion of the distillate being discarded.
2. It is essential that these steps in the isolation be carried through as rapidly as possible.
3. Larger amounts gave lower yields. The exact procedure must be followed as to time, temperature, and amounts of reagents, and the procedure completed without interruption.

3. Methods of Preparation

Ethyl benzoylacetate has been prepared by the condensation (by means of sodium ethylate) of ethyl acetate with ethyl benzoate,¹ acetophenone with ethyl carbonate,² and acetophenone with ethyl oxalate, with subsequent heating;³ by treatment of ethyl phenylpropionate⁴ or α -bromocinnamic acid⁵ with concentrated sulfuric acid, and of ethyl diazoacetate with benzaldehyde;⁶ by the condensation of benzene with the monoethyl ester of malonyl monoacid chloride and aluminum chloride,⁷ of benzoyl chloride with the product of the reaction of magnesium and ethyl chloroacetate in ether,⁸ of alcohol on benzoylacetimino ethyl

ether hydrochloride;⁹ and by the hydrolysis of ethyl benzoylacetate.¹⁰

¹ Claisen and Lowman, Ber. **20**, 651 (1887).

² Claisen, *ibid.* **20**, 655 (1887).

³ Wislicenus, *ibid.* **28**, 811 (1895).

⁴ Baeyer, *ibid.* **15**, 2705 (1882).

⁵ Michael and Browne, *ibid.* **19**, 1392 (1886).

⁶ Buchner and Curtius, *ibid.* **18**, 2371 (1885).

⁷ Marguery, Bull. soc. chim. (3) **33**, 549 (1905).

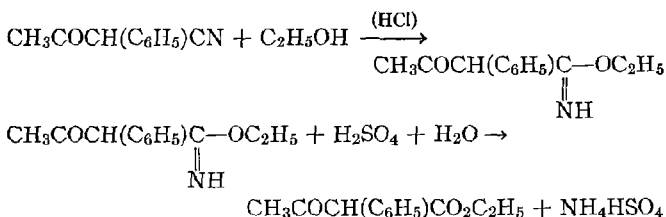
⁸ Meyer and Tögel, Ann. **347**, 55 (1906).

⁹ Haller, Bull. soc. chim. (2) **48**, 23 (1887).

¹⁰ Claisen, Ann. **291**, 71 (1896); Shriner and Schmidt, J. Am. Chem. Soc. **51**, 3636 (1929).

XIV

ETHYL α -PHENYLACETOACETATE



Submitted by R. H. KIMBALL, GEORGE D. JEFFERSON, and ARTHUR B. PIKE.
Checked by C. R. NOLLER.

1. Procedure

THE apparatus consists of a 1-l. three-necked flask with a mercury-sealed mechanical stirrer and a 6-mm. inlet tube reaching to the bottom of the flask. In the third neck is a cork bearing a low-temperature thermometer and a tube containing phosphorus pentoxide on glass wool, and calcium chloride. The inlet tube is connected to three 20-cm. drying towers, two containing phosphorus pentoxide on glass wool, and one containing calcium chloride. To the last tower is connected a 2-l. Florence flask fitted as a wash bottle with a safety tube and containing 1 l. of concentrated sulfuric acid. The Florence flask is connected to the hydrogen chloride generator described in Org. Syn. Coll. Vol. 1, 287, in which a single charge of 1.5 l. of concentrated sulfuric acid and 800 cc. of hydrochloric acid is sufficient for this preparation. A pressure equalizer should be provided between the generating flask and the funnel.

After the inlet tube is removed from the reaction flask, 400 cc. of absolute alcohol (Note 1) and 161 g. (1 mole) of dry α -phenyl-

acetoacetonitrile (m. p. 88.5–89.5°) (p. 66) are added. The neck is temporarily closed by a cork, and the nitrile dissolved by warming with stirring. The flask is then surrounded by a freezing mixture, and the solution vigorously stirred, so that any nitrile which crystallizes will be finely divided. When the temperature reaches -10° , the inlet tube is inserted, and a stream of dry hydrogen chloride passed through, with moderate stirring, at such a rate that the bubbles rising from the 6-mm. tubing in the sulfuric acid wash bottle can just be counted. This is continued for five to eight hours until the mixture is saturated (Note 2). The ice bath is then removed, stirring continued until all the solid has dissolved (about one hour), and the flask allowed to stand overnight (Note 3).

Most of the excess hydrogen chloride is removed by adding porous tile and evacuating the flask with a water pump for a half hour, while it is surrounded by a water bath maintained at about 40° . Two hundred grams of sodium carbonate is dissolved in 1200 cc. of water in a 5-l. flask, and 2 l. of cracked ice added. Into this solution the reaction mixture is poured in a thin stream with vigorous shaking, and the solution extracted at once with three 500-cc. portions of ether. The ether extracts are washed countercurrently with four 250-cc. portions of ice-cold 5 per cent sodium chloride solution to remove the alcohol and then combined in a 3-l. flask placed in an ice bath.

A solution of 100 g. of C. P. concentrated sulfuric acid in 700 cc. of water is prepared in a 5-l. flask, 1500 cc. of cracked ice added, and the mixture shaken until ice forms on the outside of the flask. After about half of this solution has been poured into the cold ether solution of the imino ether, using a funnel to remove the excess ice, the mixture is shaken for exactly fifteen seconds (Note 4), allowed to settle, and the layers separated. The remaining acid is added to the ether layer in two portions, the mixture each time being shaken for fifteen seconds, and separated. Since the ether solution, although now free of the imino ether, still contains a small amount of ethyl phenylacetoacetate, it is saved to be combined with the main portion later.

The sulfuric acid solution of the imino ether sulfate quickly

turns cloudy because of the separation of ethyl α -phenylacetoacetate. To complete the hydrolysis, the mixture is heated on the steam bath for one-half hour at the temperature at which the ether just boils (about 50°) (Note 5). It is then cooled, the ester layer separated, and the acid extracted once with 250 cc. of ether. The ether solution is washed once with 100 cc. of water which is recombined with the acid. The acid solution is replaced on the steam bath and heated for forty-five minutes after the temperature reaches $80-90^{\circ}$. After the solution is cooled and extracted as before, all ether extracts, including the original from which the imino ether was removed, are combined and washed once with 250 cc. of 5 per cent sodium bicarbonate solution, once with 250 cc. of water, and then dried over 20 g. of anhydrous sodium sulfate (Note 6). The sodium sulfate is removed by filtration and washed with ether, the ether removed from the filtrates, and the residue fractionated *in vacuo* from a 250-cc. Claisen flask having a 25-cm. fractionating side arm. The main fraction boils at $139-143^{\circ}$ at 12 mm., or $130-134^{\circ}$ at 5 mm., and weighs 103-167 g. (50-81 per cent of the theoretical amount). By fractional distillation of the fore-run, main fraction, and residue, a product boiling over a $1-2^{\circ}$ range may be obtained with no change in the yield (Note 7).

2. Notes

1. The alcohol was dried once with lime, and once with sodium, according to Note 1, Org. Syn. Coll. Vol. 1, 246.
2. More rapid saturation appreciably lowers the yield.
3. A fine precipitate, probably ammonium chloride, settles out. The most successful runs showed little or none of this precipitate.
4. Any delay at this point results in hydrolysis of some of the imino ether to the product, which stays in the ether layer.
5. Care should be taken in lifting the flask from the bath, since any mixing may cause the ether to boil out of the flask.
6. Removal of product from time to time during the course of the hydrolysis seems to improve the yield.

7. The liquid ester is an equilibrium mixture, the enol content of which is increased by distillation and falls slowly, on standing, to 30 per cent.¹ The boiling point of $145-147^{\circ}/11$ mm., recorded in the literature, is higher than any noted in the present work.

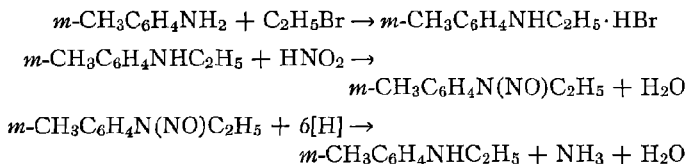
3. Methods of Preparation

Ethyl α -phenylacetoacetate can be prepared by the hydrolysis of α -phenylacetoacetonitrile in absolute alcohol with dry hydrogen chloride.¹ The present method differs in specifying neutralization of the hydrogen chloride with sodium carbonate and hydrolysis of the imino ether in aqueous sulfuric acid, so that the product separates as fast as it forms, thus being protected from further decomposition, with a considerably increased yield as the result.

¹ Beckh, Ber. **31**, 3160 (1898); Post and Michalek, J. Am. Chem. Soc. **52** 4358 (1930).

XV

N-ETHYL-*m*-TOLUIDINE



Submitted by JOHANNES S. BUCK and CLAYTON W. FERRY.
 Checked by JOHN R. JOHNSON and P. L. BARRICK.

1. Procedure

IN each of two ordinary 250-cc. (8-oz.) narrow-mouthed bottles are placed 32.1 g. (32.5 cc., 0.3 mole) of *m*-toluidine and 33 g. (23 cc., 0.3 mole) of ethyl bromide (Note 1). The bottles are sealed with rubber stoppers wired tightly in place and then allowed to stand for twenty-four hours in a 2-l. beaker filled with water at room temperature (Note 2). The white crystalline mass in each bottle is broken up and the amine is liberated by shaking with 150 cc. of 10 per cent sodium hydroxide solution and 50 cc. of ether. The contents of the two flasks are combined, the lower aqueous layer is separated and discarded, and the ether solution of the amine is washed with 150 cc. of water. When the ether is distilled from a steam bath, the crude amine (90-92 g.) is obtained.

This crude amine is added, with cooling, to a solution of 100 cc. of concentrated hydrochloric acid (sp. gr. 1.18) in 350 cc. of water. The solution of the hydrochloride is cooled in an ice bath, and stirred rapidly, while a solution of 41.5 g. (0.6 mole) of sodium nitrite in 150 cc. of water is added slowly. During this addition the temperature should not be allowed to rise above 12°. After all the nitrite has been added, the mixture is allowed

to stand for ten minutes and then extracted with three 100-cc. portions of ether. The ether is evaporated from the extract by warming gently on a steam bath and blowing a stream of air over the surface. Care must be taken to keep the temperature as low as possible during the evaporation (Note 3).

The crude nitroso compound is added gradually, with continuous shaking, to a solution of 407 g. (1.8 moles) of stannous chloride dihydrate in 420 cc. (4.8 moles) of concentrated hydrochloric acid (sp. gr. 1.18) contained in a 3-l. flask. The reaction is exothermic, and cooling is applied, if necessary, to keep the temperature below 60°. After standing for at least an hour (Note 4), the mixture is made strongly alkaline by the cautious addition of a cold solution of 520 g. (13 moles) of sodium hydroxide in about 800 cc. of water. During the addition of the alkali the mixture is agitated vigorously and cooled in running water.

The resulting milky suspension is distilled with steam until about 2 l. of distillate has collected. The distillate is saturated with sodium chloride and extracted with three 100-cc. portions of benzene. The extract is dried thoroughly overnight with flake potassium hydroxide and decanted from the spent drying agent. After removal of the solvent by distillation the amine is distilled under reduced pressure. Practically all the material distils at 111–112°/20 mm., or 115.5–117°/26 mm. The pure amine forms a practically colorless, highly refringent liquid and weighs 51–53 g. (63–66 per cent of the theoretical amount) (Note 5). It develops color rapidly on standing.

2. Notes

1. A pure grade of *m*-toluidine was used. A "practical" grade of ethyl bromide gave satisfactory results.
2. If the initial reaction is allowed to proceed too rapidly, considerable pressure may be developed in the bottles. As a safeguard against explosions it is advisable to enclose the bottles in wire mesh shields.
3. The nitroso compound decomposes on warming or on standing. It should not be stored but treated at once with the reducing agent.

4. The mixture may be allowed to stand for a longer period (overnight) without harm. Frequently a granular precipitate of a tin complex of the amine separates.

5. Other *N*-alkyl-*m*-toluidines may be prepared by practically the same procedure. The submitters report that *n*-propyl, *iso*-propyl, and *n*-butyl derivatives are obtained readily from *m*-toluidine and the appropriate alkyl iodides (rather than the bromides). In these cases the alkylation is effected by placing the sealed bottle in a beaker of water which is warmed gradually to 70–80° and kept in a warm place until the reaction is completed; usually several days are required.

3. Methods of Preparation

N-Ethyl-*m*-toluidine has been obtained by passing *m*-toluidine and ethyl alcohol over a catalyst at high temperatures,¹ and by the use of ethyl *p*-toluenesulfonate² as an alkylating agent. The present method of purification is a modification of a general procedure for secondary amines developed by Diepolder.³

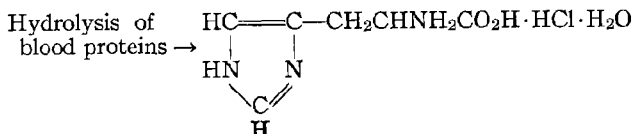
¹ Mailhe and Codon, Compt. rend. **172**, 1417 (1921); Mailhe, Fr. pat. 23,891 [Chem. Zentr. IV, 760 (1922)].

² Finzi, Ann. chim. applicata **15**, 41 (1925).

³ Diepolder, Ber. **32**, 3514 (1899).

XVI

L-HISTIDINE MONOHYDROCHLORIDE



Submitted by G. L. FOSTER and D. SHEMIN.

Checked by JOHN R. JOHNSON, H. E. CARTER, and P. L. BARRICK.

1. Procedure

IN a large round-bottomed flask are placed 1400 g. of dried blood corpuscle paste (Note 1) and 4.5 l. of concentrated hydrochloric acid (sp. gr. 1.18). The flask is warmed on a steam bath until the protein has dissolved, and the mixture is boiled gently under reflux for eighteen to twenty hours. After the hydrolysate has been concentrated under reduced pressure to a thick paste, the distillation is continued with the slow addition of a liter of water, thus eliminating most of the excess hydrochloric acid. The residue is taken up in 8 l. of warm water, cooled, and neutralized to pH 4.4-4.6 (methyl orange or bromcresol green) by the addition of concentrated sodium hydroxide solution (Note 2). After the mixture has stood overnight, the precipitated pigment is removed by filtering through a large Buchner funnel, fitted with two layers of filter paper and a 2-mm. layer of infusorial earth. The filtrate, which is dull red in color, is decolorized by warming and stirring for ten minutes with 60 g. of Norite.

The pale yellow filtrate and washings from the Norite are diluted to 25 l. with tap water, and a solution of 600 g. of mercuric chloride in 2 l. of hot 95 per cent alcohol is added, with stirring. A concentrated solution of sodium carbonate (cor-

responding to about 350 g. of anhydrous sodium carbonate) is added slowly, with stirring, until the mixture reaches pH 7.0-7.5 (phenol red or litmus). After settling for several hours, preferably overnight, the supernatant liquid is siphoned off, and the crock refilled with water to the original volume (Note 3). The mixture is allowed to settle, the wash liquid siphoned off, and the precipitate washed twice more in the same fashion. After the third washing, the supernatant liquid is siphoned off, and the precipitate collected with suction on a large Buchner funnel fitted with two layers of filter paper and a 2-mm. layer of infusorial earth.

The moist histidine-mercury complex is suspended in 5 l. of water and stirred vigorously, while a stream of hydrogen sulfide is introduced. When precipitation of mercuric sulfide is complete, the suspension becomes uniformly black and settles sharply on standing. The filtrate and washings from the mercuric sulfide (Note 4) are concentrated under reduced pressure to a volume of about 1 l. and cleared with 5 g. of Norite. The filtrate and washings from the Norite are concentrated further to a volume of about 250 cc. and mixed with three volumes of 95 per cent alcohol. Crystallization is induced by cooling the solution and scratching the walls of the vessel; the histidine monohydrochloride separates in plates. After the material has remained in an ice chest for three or four days, the crystals are separated by suction filtration. The yield of crude histidine monohydrochloride is 85-90 g. The filtrate, on standing for several weeks in an ice chest, usually deposits an additional 4-5 g. of material.

The crude product is dissolved in five times its weight of water, and after clearing with a little Norite the solution is diluted with one and one-half volumes of 95 per cent alcohol. The product separates in well-formed, snow-white crystals, and after standing for several days in an ice chest is collected with suction on a Buchner funnel. The yield of purified histidine monohydrochloride is 75-80 g. (Note 5). The compound melts at 251-252°, with decomposition. The amino acid is not racemized by the procedure employed, and shows the characteristic optical activity, $[\alpha]_D^{26} = +8.0^\circ$, in the presence of three moles of

hydrochloric acid. The recrystallized product is usually analytically pure, and shows the correct Van Slyke amino nitrogen content. Occasionally a second recrystallization is necessary to obtain analytically pure material.

2. Notes

1. Commercial "dried blood corpuscle paste" obtained from Armour and Company, Chicago, was used in this preparation. This paste contains about 15 per cent of moisture and ash, and 200 g. contains about the same amount of crude protein as 1 l. of fresh beef blood (170 g. protein per liter).

If fresh blood is used in this preparation, it is convenient to remove much of the water in the following way. Seven liters of beef blood in a 12-l. round-bottomed flask is treated with 50 cc. of glacial acetic acid, and heated on a steam bath, with occasional stirring, until a thick, pasty coagulum results. About 4 l. of water is removed by distillation under reduced pressure, using a steam bath, and the residue is hydrolyzed as described above.

2. About 600 cc. of 50 per cent sodium hydroxide is required for neutralization. An excess of alkali should be avoided.

3. Occasionally the histidine-mercury complex settles slowly. In this case the supernatant liquid may be siphoned off and filtered. The small amount of material collected on the filter is then returned to the main portion.

4. The mercuric sulfide may be saved and converted to metallic mercury or mercuric chloride by the usual procedures.

5. About 10 g. of crude histidine monohydrochloride may be recovered from the mother liquor by evaporating under reduced pressure to 50-60 cc. and adding one and one-half volumes of 95 per cent alcohol. On recrystallization 8-9 g. of pure material is obtained.

3. Methods of Preparation

The preparation of histidine by the hydrolysis of hemoglobin and precipitation with mercuric chloride in alkaline solution was

first carried out by Fränkel.^{1,2} Histidine can also be precipitated as the silver derivative.³

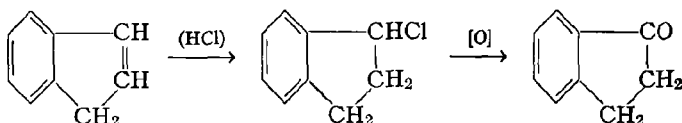
¹ Fränkel, *Monatsh.* **24**, 229 (1903).

² Abderhalden, Fleischmann, and Irion, *Fermentforschung* **10**, 447 (1928).

³ Kossel, *Zeit. physiol. Chem.* **25**, 177 (1898); Vickery and Leavenworth, *J. Biol. Chem.* **78**, 627 (1928).

XVII

α -HYDRINDONE (1-Indanone)



Submitted by R. A. PACAUD and C. F. H. ALLEN.
Checked by L. F. FIESER and W. P. CAMPBELL.

1. Procedure

A 250-cc. flask fitted with an inlet tube reaching to the bottom, a thermometer, and an exit tube for conducting away unused gas, is immersed in an ice-water bath, and to it is added 80 g. (0.69 mole) of freshly distilled indene (Note 1). With the temperature of the liquid kept at 5–10°, dry hydrogen chloride (Org. Syn. Coll. Vol. 1, 287) is passed in at a moderate rate until 24–27 g. of the gas has been absorbed. The addition takes from eight to ten hours and requires little attention from the operator. The crude α -chlorohydrindene is then transferred to a 250-cc. Claisen flask and distilled at diminished pressure. After a small fore-run (5–10 g.) containing indene, the fraction of α -chlorohydrindene boiling at 90–103°/15 mm. is collected; the yield is 80–90 g. (Note 2).

In a 500-cc. three-necked flask, fitted with a stirrer, thermometer, and dropping funnel, is placed 100 g. (1 mole) of chromic anhydride dissolved in 100 cc. of water, and 100 cc. of glacial acetic acid is added. The α -chlorohydrindene is then admitted through the funnel at such a rate as to keep the temperature at 35–40°, the flask being cooled externally. This addition takes about one and one-half hours, and after it is complete, stirring is

continued for fifteen minutes before the mixture is poured into a large beaker and diluted with 300 cc. of water. After the acid present is neutralized by the addition of solid sodium carbonate (Note 3), the α -hydrindone is expelled from the mixture by steam distillation, care being taken to avoid entrainment of froth at the beginning of the process. When about 2.5 l. of distillate has been collected, the solution again begins to froth. The operation is stopped at this point, since further distillation does not yield an appreciable quantity of product. The α -hydrindone usually solidifies as soon as the distillate is chilled, giving a mixture of colorless crystals and a yellow solid; the product is collected after thorough cooling in an ice bath. This moist solid is dissolved in 200 cc. of benzene, and the solution subjected to distillation until free from water. After the benzene is removed by vacuum distillation on the steam bath, the α -hydrindone is distilled. It boils at $125-126^{\circ}/17$ mm., and the distillate is a pale yellow solid, m. p. $39-41^{\circ}$. The yield is 46-55 g. (50-60 per cent of the theoretical amount, based on the indene used) (Notes 4 and 5).

2. Notes

1. If technical indene is employed, the fraction boiling at $178-182^{\circ}$ is suitable for the preparation. The checkers used indene, b. p. $181.6-183.3^{\circ}$, obtained from the Barrett Company, New York City.

2. Most of the material distils at $100-103^{\circ}/15$ mm., but the yield of α -hydrindone is increased by using the material collected over the wider range.

3. An excess of sodium carbonate promotes foaming during the distillation, and is to be avoided. Since the neutral point is not easily recognized with test paper, the carbonate is added in decreasing amounts, until a fresh portion is no longer decomposed with gas evolution.

4. It is not practical to dry the steam-distilled product in the air, because α -hydrindone has such a high vapor pressure that the loss is appreciable. Drying can be accomplished in a vacuum desiccator, but this takes several days. The distillation

specified gives a completely anhydrous product with the loss of no more than 2-5 g.

5. Crystallization is conveniently accomplished by dissolving the α -hydrindone in alcohol (1 cc. per gram) at room temperature, adding water until solid just begins to separate, and cooling to 0°. The substance crystallizes either as long plates or as leaflets.

3. Methods of Preparation

α -Hydrindone has been made in good yields by heating indene bromohydrin with dilute sulfuric acid.¹ The only other practical methods of obtaining it involve the cyclization of hydrocinnamyl chloride with ferric chloride² or aluminum chloride,³ or the interaction of acrylyl chloride with benzene in the presence of aluminum chloride.⁴ The above procedure is essentially that of Hückel, Sachs, Yantschulewitsch, and Nerdel.⁵

¹ Porter and Suter, J. Am. Chem. Soc. **57**, 2022 (1935).

² Wedekind, Ann. **323**, 246 (1902).

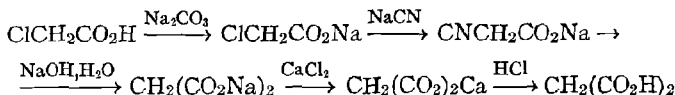
³ Kipping, J. Chem. Soc. **65**, 480 (1894).

⁴ Moureu, Bull. soc. chim. (3) **9**, 568 (1893); Ann. chim. (7) **2**, 145 (1894); Kohler, Am. Chem. J. **42**, 375 (1909).

⁵ Hückel, Sachs, Yantschulewitsch, and Nerdel, Ann. **518**, 155 (1935).

XVIII

MALONIC ACID



Submitted by NATHAN WEINER.

Checked by C. R. NOLLER and M. E. SYNERHOLM.

1. Procedure

In a 5-l. round-bottomed flask, 500 g. (5.3 moles) of chloroacetic acid (Note 1) is dissolved in 700 cc. of water. The solution is warmed to 50°, neutralized with 290 g. (2.7 moles) of anhydrous sodium carbonate, and again cooled to room temperature. Meanwhile, 294 g. (6.0 moles) of sodium cyanide (97 per cent) is dissolved in 750 cc. of water warmed to 55°, the solution is cooled to room temperature, and then added to the sodium chloroacetate solution, with rapid mixing of the two solutions and cooling under the water tap. When the solutions are completely mixed, the cooling is stopped and the temperature allowed to rise. When it reaches 95°, the solution is cooled by adding 200 cc. of ice water, and this is repeated, if necessary, until the temperature no longer rises (Note 2). The solution is then heated on the steam bath for one hour to ensure completion of the reaction.

At the end of this time, the solution is cooled to room temperature and 240 g. (6 moles) of solid U. S. P. sodium hydroxide is slowly dissolved in it. When solution is complete, the reaction mixture is again heated on the steam bath under a hood. When the temperature reaches 60–70°, evolution of ammonia begins and becomes more vigorous with rise in temperature. The major part of the evolution is complete in forty-five minutes, but the

solution is heated for at least three hours, and the last traces of ammonia removed by bubbling steam through the hot solution for forty-five to sixty minutes more.

A solution of 600 g. of anhydrous calcium chloride in 1800 cc. of water warmed to 40° is added slowly with rapid mixing to the hot sodium malonate solution. A cheese-like precipitate of calcium malonate is formed immediately and becomes coarsely crystalline on standing for twenty-four hours. After the supernatant solution is decanted, the calcium malonate is washed by decantation four or five times with 500-cc. portions of cold water. It is then transferred to a filter, sucked as dry as possible, and dried in the air, or at $45-50^{\circ}$, to constant weight. The yield is 800-900 g.

The dry calcium malonate is placed in a 3-l. round-bottomed flask with sufficient (750-1000 cc.) alcohol-free ether (Note 3) to make a paste which can be stirred. The flask is surrounded by an ice bath, and the well-stirred salt is treated with 1 cc. of 12 *N* hydrochloric acid for each gram of salt. After the acid has been added slowly through a dropping funnel, the solution is transferred to a continuous extractor (Note 4) and extracted with ether until no more malonic acid is obtained. The product, as obtained from the undried ether solution by concentration, filtration, and drying in the air, melts at 130° or higher and is sufficiently pure for most purposes. The yield is 415-440 g. (77-82 per cent of the theoretical amount).

2. Notes

1. A freshly distilled product boiling over a 3° range was used.
2. If the reaction between the cyanide and the chloroacetate becomes too vigorous, hydrogen cyanide is liberated and partly changed to a brown material, and a corresponding quantity of glycolate is formed. If the temperature of the reaction mixture is allowed to go above 95° spontaneously, the liquid may boil so vigorously and suddenly as to escape from the flask despite the large extra volume provided.
3. Ether is used to avoid unnecessarily increasing the volume

of aqueous solution to be extracted. This ether may be used for further extraction. It is necessary to use alcohol-free ether to avoid esterifying the malonic acid during the protracted extraction period.

4. A convenient type of extractor, used in this preparation, was made as follows by modifying that described by J. Friedrichs:¹ a 20-cm. calcium chloride tower, or other narrow-necked cylinder with a volume of about 1300 cc., was used as an extraction chamber. The mantle-tube, conducting the ether vapors to an Allihn condenser, was made of 25-mm. tubing and was about 50 cm. long. The goose-neck to the extraction flask, of 14-mm. tubing, was sealed to the mantle-tube about 8 cm. from the bottom end. The inner tube was of 14-mm. tubing, about 65 cm. long, flanged at the top to a diameter of about 20 mm. A Witt filter plate of the proper diameter may be sealed into the bottom of the tube to make the ether pass up through the water in a stream of fine bubbles, or this can also be accomplished by sealing off the bottom of the tube and piercing it with 3-6 pinholes. The mantle-tube was fitted to the chamber by a properly bored rubber stopper, the condenser to the top of the mantle-tube, and the 500-cc. extraction flask to the goose-neck by charred cork stoppers. With this apparatus 395-400 g. of malonic acid was extracted in seventy-two hours, the ether being changed every twenty-four hours, and the final traces were extracted after an additional twenty-four hours.

3. Methods of Preparation

Malonic acid has been made by the hydrolysis of malononitrile with concentrated hydrochloric acid,² by the hydration of carbon suboxide,³ and by the hydrolysis of cyanoacetic acid⁴ and its esters⁵ with potash. A method for the preparation of calcium malonate from chloroacetic acid and potassium cyanide is described by Fischer.⁶ Conrad⁷ liberated malonic acid from calcium malonate, so prepared, with oxalic acid. v. Miller,⁸ Grimaux and Tscherniak,⁹ and Bourgoin¹⁰ prepared malonic acid from chloroacetic acid and potassium cyanide, Petriev¹¹ from

ethyl chloroacetate and potassium cyanide, and Franchimont¹² from ethyl bromoacetate and potassium cyanide.

¹ Friedrichs, *Chem. Fabrik* **1**, 91 (1928). An exact reproduction may be found in the apparatus catalogue of A. H. Thomas Company, Philadelphia, 1931 Edition, p. 356, article 5006.

² Henry, *Compt. rend.* **102**, 1396 (1886).

³ Diels and Wolf, *Ber.* **39**, 696 (1906).

⁴ Kolbe, *Ann.* **131**, 349 (1864).

⁵ H. Müller, *ibid.* **131**, 352 (1864).

⁶ Fischer, "Introduction to the Preparation of Organic Compounds," p. 75. Translated from the eighth German edition by R. V. STANDORD, D. Van Nostrand and Company, New York.

⁷ Conrad, *Ann.* **204**, 126 (1880).

⁸ v. Miller, *J. prakt. Chem.* (2) **19**, 326 (1879).

⁹ Grimaux and Tcherniak, *Bull. soc. chim.* (2) **31**, 338 (1879).

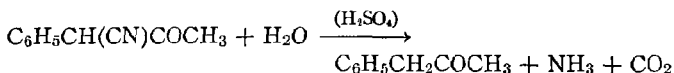
¹⁰ Bourgoin, *ibid.* (2) **33**, 574 (1880).

¹¹ Petriev, *J. Russ. Phys. Chem. Soc.* **10**, 64 (1878).

¹² Franchimont, *Ber.* **7**, 216 (1874).

XIX

METHYL BENZYL KETONE (Phenylacetone)



Submitted by PERCY L. JULIAN and JOHN J. OLIVER.
Checked by C. R. NOLLER.

1. Procedure

THREE HUNDRED FIFTY cubic centimeters of concentrated sulfuric acid (Note 1) is placed in a 3-l. flask and cooled to -10° . The total first crop of moist α -phenylacetoacetonitrile obtained according to the procedure on p. 66 (corresponding to 188–206 g., or 1.2–1.3 moles of dry product) is added slowly, with shaking, the temperature being kept below 20° . After all is added the flask is warmed on the steam bath until solution is complete and then for five minutes longer. The solution is cooled to 0° , 1750 cc. of water added rapidly, and the flask placed on a vigorously boiling water bath and heated for two hours, with occasional shaking. The ketone forms a layer and after cooling is separated and the acid layer extracted with 600 cc. of ether. The oil and ether layers are washed successively with 100 cc. of water, the ether combined with the oil and dried over 20 g. of anhydrous sodium sulfate. The sodium sulfate is collected on a filter, washed with ether, and discarded. The ether is removed from the filtrates, and the residue distilled from a modified Claisen flask with a 25-cm. fractionating side arm. The fraction boiling at $109\text{--}112^\circ$ at 24 mm. is collected; it weighs 125–150 g. (77–86 per cent of the theoretical amount) (Note 2).

2. Notes

1. If pure dry α -phenylacetoacetonitrile is used, half its weight of water should be added to the sulfuric acid, or charring will take place on the steam bath.

2. Usually almost the entire crude product distils in this range with practically no fore-run or residue. Occasionally, however, as much as 30 g. of high-boiling residue, chiefly unchanged nitrile, is obtained. When this happens the yield is correspondingly decreased.

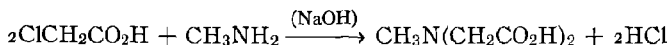
3. Methods of Preparation

Other methods of preparation have been reviewed in an earlier volume.¹

¹ Org. Syn. 18, 50.

XX

METHYLIMINODIACETIC ACID



Submitted by G. J. BÉCHET.

Checked by JOHN R. JOHNSON and P. L. BARRICK.

1. Procedure

In a 2-l. flask provided with a mechanical stirrer, separatory funnel, and thermometer, are placed 189 g. (2 moles) of chloroacetic acid and 150 cc. of water. The flask is cooled in ice water, and a cold solution of 160 g. (4 moles) of sodium hydroxide in 500 cc. of water is added, with stirring, at such a rate that the temperature does not exceed 30° (Note 1). After all the alkali has been added, the cooling bath is removed, and an aqueous solution (Note 2) containing 31 g. (1 mole) of methylamine is added slowly. The reaction is exothermic, and the temperature is kept below 50° by occasional immersion of the flask in ice water. After all the methylamine has been added, the solution is allowed to stand for two hours to complete the reaction.

A solution of 257 g. (1.05 moles) of barium chloride dihydrate in about 500 cc. of hot water is added to the reaction mixture, with vigorous shaking, and the mixture is heated on a steam bath for one-half hour. A heavy precipitate of the barium salt of the amino acid separates at once. After cooling to room temperature, the barium salt is collected on a suction filter, transferred to a beaker, and washed with two 250-cc. portions of hot water (80°). After drying at 100°, the barium salt weighs 225–230 g. (80–82 per cent of the theoretical amount).

The dry barium salt is placed in a 2-l. flask provided with a mechanical stirrer, 600 cc. of water is added, and the mixture

heated to boiling. The calculated quantity of 5 *N* sulfuric acid (Note 3) is introduced gradually from a separatory funnel into the well-stirred mixture over a period of about one hour. The mixture is then centrifuged or filtered with suction (Note 4) through a thin layer of fuller's earth. The barium sulfate precipitate is transferred to a beaker and extracted with two 250-cc. portions of boiling water. The filtrate and washings are transferred to a distilling flask placed in a water bath and concentrated under reduced pressure to a volume of 175–200 cc. (Note 5). The syrupy residue is poured into a large beaker and treated with 500 cc. of absolute methyl alcohol. Crystals of the acid begin to appear at once. The mixture is allowed to stand for three or four hours in an ice bath to complete the precipitation, and the crystalline solid is separated by filtration with suction. After being washed with two 75-cc. portions of methyl alcohol, the product is dried at 100°. The methyliminodiacetic acid forms fine, white crystals, m. p. 215° (uncorr.), and weighs 92–105 g. (63–71 per cent of the theoretical amount).

If an especially pure product is desired, the acid may be reprecipitated by dissolving in an equal weight of warm water and adding three volumes of methyl alcohol. The loss in purification is 4–5 per cent.

2. Notes

1. The temperature must be controlled to avoid formation of glycolic acid. One-half of the alkali is sufficient to neutralize the acid, and the remainder may be added rapidly without danger of raising the temperature.

2. Technical aqueous methylamine solution (28–33 per cent) may be used. The amine content should be determined by titration with standard acid.

3. The barium salt requires 1.416 cc. of 5 *N* sulfuric acid per gram. The acid should be titrated before use.

4. If unchanged barium methyliminodiacetate remains in solution, it peptizes the barium sulfate and the filtration is likely to be troublesome. If colloidal barium sulfate is encountered, it

is advisable to add a slight excess (less than 1 per cent) of sulfuric acid and continue the heating for twenty minutes longer. Traces of sulfate in the final product may be removed, if necessary, by reprecipitation of the acid with methyl alcohol.

5. The residue should have a syrupy consistency but should be fluid enough to be poured freely from the flask.

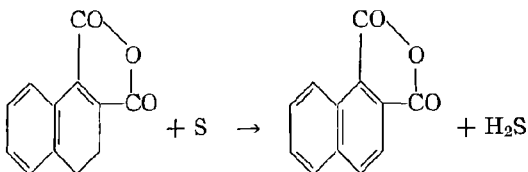
3. Methods of Preparation

Methyliminodiacetic acid has been prepared by the action of methylamine on formaldehyde cyanohydrin, subsequent hydrolysis of the dinitrile with barium hydroxide, and regeneration from the barium salt with sulfuric acid.¹ This method was found by the submitter to be much less satisfactory than the procedure given above.

¹ Eschweiler, Ann. **279**, 39 (1894).

XXI

1,2-NAPHTHALIC ANHYDRIDE



Submitted by E. B. HERSHBERG and L. F. FIESER.

Checked by C. R. NOLLER and S. KINSMAN.

1. Procedure

In a 50-cc. Claisen distilling flask with a 50-cc. sealed-on distilling flask as a receiver are placed 20 g. (0.1 mole) of 3,4-dihydro-1,2-naphthalic anhydride (p. 24) and 3.2 g. (0.1 gram atom) of sulfur. After the flask is immersed in a bath (Note 1) previously heated to 230–235° and shaken until the globule of sulfur has dissolved (fifteen to twenty minutes), the temperature is raised to 250° for thirty minutes (Note 2). The residue is distilled under reduced pressure (Note 3), and the distillate crystallized from 150 cc. of benzene, to which 50 cc. of ligroin (b. p. 60–80°) has been added at the boiling point. The yield is 15–18 g. (76–91 per cent of the theoretical amount) of light yellow needles melting at 166–167°.

2. Notes

1. A Wood's metal bath or a mixture (m. p. about 150°) of ten parts of potassium nitrate and seven and one-half parts of sodium nitrite may be used.

2. If the heating at 250° is continued until hydrogen sulfide is no longer evolved (about ten hours), the product, after recryst-

tallization, is lighter in color and shrinks less before the melting point is reached.

3. The material comes over between 210° and 215° at 12-13 mm. with the bath at 260° .

3. Methods of Preparation

1,2-Naphthalic anhydride has been prepared by the hydrolysis of the dinitrile of 1,2-naphthalic acid,¹ by the oxidation of suitably substituted hydrocarbons or ketones,² or by the dehydrogenation of the 3,4-dihydro compound with bromine³ or with sulfur.⁴

¹ Cleve, Ber. **25**, 2475 (1892); Waldmann, J. prakt. Chem. **127**, 195 (1930); Cook, J. Chem. Soc. **1932**, 456.

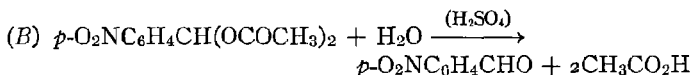
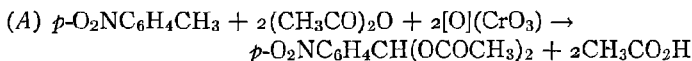
² Freund and Fleischer, Ann. **399**, 186, 210 (1913); Kruber and Schade, Ber. **68**, 11 (1935).

³ von Auwers and Möller, J. prakt. Chem. (2) **109**, 141 (1925).

⁴ Fieser and Hershberg, J. Am. Chem. Soc. **57**, 1851 (1935).

XXII

p-NITROBENZALDEHYDE



Submitted by S. V. LIEBERMAN and RALPH CONNOR.

Checked by JOHN R. JOHNSON and E. A. CLEVELAND.

1. Procedure

(A) *p*-Nitrobenzaldiacetate.—In a 2-l. three-necked, round-bottomed flask equipped with a mechanical stirrer and a thermometer, and surrounded by an ice-salt bath, are placed 570 cc. (600 g.) of glacial acetic acid, 565 cc. (612 g., 6.0 moles) of acetic anhydride (Note 1), and 50 g. (0.36 mole) of *p*-nitrotoluene (Note 2). To this solution is added slowly, with stirring, 85 cc. (1.5 moles) of concentrated sulfuric acid (Note 3). When the mixture has cooled to 5°, 100 g. (1.0 mole) of chromium trioxide (Note 2) is added in small portions at such a rate that the temperature does not rise above 10° (Note 4), and stirring is continued for ten minutes after the chromium trioxide has been added. The contents of the flask is poured into two 3-l. beakers two-thirds filled with chipped ice, and cold water is added until the total volume is 5–6 l. The solid is separated by suction filtration and washed with cold water until the washings are colorless. The product is suspended in 500 cc. of cold 2 per cent sodium carbonate solution and stirred mechanically. After thorough mixing, the solid is collected on a filter (Note 5), washed with cold water, and finally with 20 cc. of cold alcohol. The product, after drying in a vacuum desiccator, weighs 44–49 g.

(48-54 per cent of the theoretical amount), m. p. 120-122° (Note 6).

The crude material is suitable for hydrolysis, and for other reactions, without further purification. The pure diacetate may be obtained by recrystallizing from 150 cc. of hot alcohol. The hot solution is filtered through a fluted filter to remove insoluble impurities. The yield of pure *p*-nitrobenzaldiacetate is 43-46 g. (47-50 per cent of the theoretical amount), m. p. 125-126°.

(B) *p*-Nitrobenzaldehyde.—A mixture of 45 g. (0.18 mole) of crude *p*-nitrobenzaldiacetate, 100 cc. of water, 100 cc. of alcohol, and 10 cc. of concentrated sulfuric acid is refluxed for thirty minutes, filtered through a fluted filter, and the filtrate chilled in an ice bath. The crystals are separated by suction filtration, washed with cold water, and dried in a vacuum desiccator. The first crop weighs 22-24 g. (82-89 per cent of the theoretical amount), m. p. 106-106.5°. A second crop amounting to 2-3 g. is obtained by diluting the filtrate with about 300 cc. of water. The total yield is 24-25.5 g. (89-94 per cent of the theoretical amount) (Note 6).

2. Notes

1. The "practical" grade of acetic anhydride (95 per cent) gave yields as high as those obtained with 99-100 per cent acetic anhydride.

2. The *p*-nitrotoluene used was a "practical" grade, m. p. 50-51°. The chromium trioxide was a U. S. P. grade of 98 per cent purity.

3. If the sulfuric acid is added too rapidly, charring occurs.

4. It is essential that the temperature of the reaction mixture be maintained below 10°. If the oxidant is added so rapidly that this temperature is exceeded, the yield is lowered considerably. With a good ice-salt bath, the time required for the addition is forty-five to sixty minutes.

5. By acidification of the sodium carbonate washings, 7-10 g. of *p*-nitrobenzoic acid, m. p. 242-243°, is obtained.

6. The submitters report that *p*-bromobenzaldehyde may be prepared by the same procedure, substituting 62 g. (0.37 mole)

of *p*-bromotoluene for the *p*-nitrotoluene and carrying out the oxidation and isolation in the same manner. The yield of crude *p*-bromobenzaldiacetate is 51–64 g. (48–60 per cent of the theoretical amount), m. p. 90–92°. The pure diacetate is obtained by dissolving the crude product in 150 cc. of hot alcohol, filtering through a fluted filter, and cooling. Filtration gives 39–52 g. of pure material, m. p. 94–95°. A second crop is obtained by diluting the filtrate. The total yield is 47–56 g. (46–54 per cent of the theoretical amount, based on the bromotoluene). The crude product is hydrolyzed to *p*-bromobenzaldehyde by refluxing 45 g. (0.157 mole) with 100 cc. of water, 150 cc. of alcohol, and 10 cc. of concentrated sulfuric acid, filtering through a fluted filter, cooling, and filtering with suction. A second crop is obtained by diluting the filtrate with about 300 cc. of water. The product weighs 24–28 g. (83–96 per cent of the theoretical amount), m. p. 55–57°.

3. Methods of Preparation

p-Nitrobenzaldehyde has been prepared from *p*-nitrotoluene by treatment with isoamyl nitrite in the presence of sodium methylate,¹ by oxidation with chromyl chloride,² cerium dioxide,³ or chromium trioxide in the presence of acetic anhydride.⁴ It can also be prepared by the oxidation of *p*-nitrobenzyl chloride,⁵ *p*-nitrobenzyl alcohol,⁶ or the esters of *p*-nitrocinnamic acid.⁷

¹ Angeli and Angelico, Atti accad. Lincei (5) 8, II, 28 (1899).

² Richter, Ber. 19, 1060 (1886); Law and Perkin, J. Chem. Soc. 93, 1633 (1908).

³ Hoechstler Farbw., Ger. pat. 174,238 [Frdl. 8, 150 (1905–1907)].

⁴ Thiele and Winter, Ann. 311, 353 (1900).

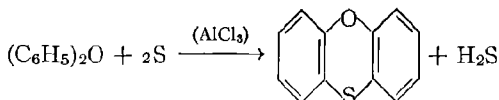
⁵ Fischer and Greiff, Ber. 13, 669 (1880); Schmidt, Ger. pat. 15,881 [Frdl. 1, 60 (1877–1887)].

⁶ Cohen and Harrison, J. Chem. Soc. 71, 1057 (1897); Walter, Ger. pat. 118,567 [Frdl. 6, 131 (1900–1902)].

⁷ Baeyer, Ger. pat. 15,743 [Frdl. 1, 60 (1877–1887)].

XXIII

PHENOXTHIN



Submitted by C. M. SUTER and CHARLES E. MAXWELL.
 Checked by REYNOLD C. FUSON and E. A. CLEVELAND.

1. Procedure

In a 5-l. flask are placed 1886 g. (1750 cc., 11 moles) of phenyl ether (Note 1), 256 g. (8 moles) of sulfur (flowers), and 510 g. (3.8 moles) of anhydrous aluminum chloride. The reactants are mixed well by shaking the flask vigorously; the mixture assumes a purple color. The flask is fitted with a water-cooled reflux condenser (Note 2) and heated on the steam bath in an efficient hood. The evolution of hydrogen sulfide, vigorous at first, becomes slow after one and one-half hours. After the heating has been continued for a total time of four hours, with occasional shaking, the reaction mixture is poured slowly, with stirring, into a 4-l. beaker half filled with ice to which 250 cc. of concentrated hydrochloric acid has been added. More ice is added if necessary. The flask is rinsed with water and the rinsings added to the main product. After the two layers are separated the water layer is discarded and the phenyl ether-phenoxthin layer dried overnight with calcium chloride. This mixture is then distilled at 5 mm. pressure from a 3-l. special Claisen flask having a well-lagged 18-in. column. After removal of the phenyl ether the fraction boiling at 140–160°/15 mm., practically all of which comes over at 150–152°, is collected as phenoxthin (Note 3). The yield is 700 g. (87 per cent of the theoretical amount). This

material, which is somewhat colored and has a strong odor, is purified by crystallization from 1200–1500 cc. of boiling methyl alcohol, care being taken to chill rapidly and stir well to prevent the product from separating as an oil. The loss on crystallization is about 3 per cent, the dried material melting at 56–57° (Note 4). A second crystallization gives a product melting about one degree higher.

2. Notes

1. The commercial "diphenyl oxide" is satisfactory.
2. The condenser returns to the flask a small amount of phenyl ether, which would otherwise be carried away by the hydrogen sulfide.
3. The fore-run of phenyl ether, b. p. 98–101°/5 mm., may be used in subsequent runs. Other boiling points are: phenyl ether, 134–137°/15 mm., 259–262°/745 mm.; and phenoxthin, 180–183°/15 mm., 311°/745 mm. Fractionation at 15 mm. gives a lower yield with a larger amount of tarry residue remaining in the flask than when the lower pressure (5 mm.) is used.
4. A pure sample melts at 57.5–58°.

3. Methods of Preparation

Phenoxthin has been obtained by a series of reactions utilizing thiocatechol and 3,5-dinitro-4-chlorobenzoic acid¹ as the starting materials, from phenoxtellurin and sulfur,² and by the action of sulfur and aluminum chloride upon phenyl ether.³

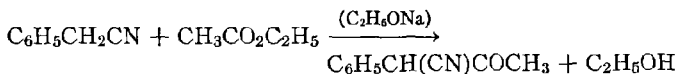
¹ Mauthner, Ber. **39**, 1340 (1906).

² Drew, J. Chem. Soc. **1928**, 511.

³ Ferrario, Bull. soc. chim. (4) **9**, 536 (1911); Ackermann, Ger. pat. 234,743 [Chem. Zentr. I, 1768 (1911)]; Suter, McKenzie, and Maxwell, J. Am. Chem. Soc. **58**, 717 (1936); Bennett, Lesslie, and Turner, J. Chem. Soc. **1937**, 444; Suter and Green, J. Am. Chem. Soc. **59**, 2578 (1937).

XXIV

α -PHENYLACETOACETONITRILE
(Acetobenzyl Cyanide)



Submitted by PERCY L. JULIAN, JOHN J. OLIVER, R. H. KIMBALL, ARTHUR B. PIKE, and GEORGE D. JEFFERSON.

Checked by C. R. NOLLER and MARTIN SYNERHOLM.

1. Procedure

A SOLUTION of sodium ethylate is prepared from 60 g. (2.6 gram atoms) of clean sodium and 700 cc. of absolute alcohol (Note 1) in a 2-l. round-bottomed flask, equipped with a reflux condenser. To the hot solution is added a mixture of 234 g. (2 moles) of pure benzyl cyanide (Note 2) and 264 g. (3 moles) of dry ethyl acetate (Note 3). The mixture is thoroughly shaken, the condenser closed with a calcium chloride tube, and the solution heated on the steam bath for two hours before standing overnight (Note 4). The next morning the mixture is stirred with a wooden rod to break lumps, cooled in a freezing mixture to -10° , and kept at this temperature for two hours. The sodium salt is collected on a 6-in. Buchner funnel and washed four times on the funnel with 250-cc. portions of ether. The filter cake is practically colorless and corresponds to 250-275 g. of dry sodium salt, or 69-76 per cent of the calculated amount. The combined filtrates are placed in the freezing mixture until they can be worked up as indicated below.

The sodium salt still wet with ether is dissolved in 1300 cc. of distilled water at room temperature, the solution cooled to 0° , and the nitrile precipitated by adding slowly, with vigorous shaking, 90 cc. of glacial acetic acid, while the temperature is kept below 10° . The precipitate is separated by suction filtration

and washed four times on the funnel with 250-cc. portions of water. The moist cake weighing about 300 g. (Note 5) corresponds to 188-206 g. (59-64 per cent) of dry colorless α -phenylacetoacetonitrile, m. p. 87-89°, which is suitable for most purposes.

If it is desired to recrystallize the crude product, the moist cake is dissolved in 100 cc. of hot methyl alcohol and the solution filtered and cooled, with stirring, to -10°. The crystals are separated by suction filtration and washed once on the filter with 40 cc. of methyl alcohol cooled to -10°. When dry, the product weighs 173-191 g. (54-60 per cent) and melts at 88.5-89.5°.

The filtrates and washings from the separation of the sodium salt are placed in a 5-l. flask and diluted with ice-cold water until the flask is full; the lower layer is removed almost completely by siphoning, most of the ether removed by decantation, and the remainder separated in a separatory funnel. The aqueous layer is extracted twice in a similar manner with 500-cc. portions of ether, and the ether extracts discarded. The ether remaining in the aqueous layer is removed under diminished pressure by drawing air through the solution for one hour with a suction pump, and the α -phenylacetoacetonitrile is precipitated by adding 60 cc. of glacial acetic acid. If an oil is thrown out, the flask is placed in an ice bath until the precipitate is crystalline. The crystals are separated by suction filtration and washed four times on the funnel with 50-cc. portions of water. When dry the tan-colored product weighs 50-55 g. and melts at 83-86°. It is dissolved in the methyl alcohol mother liquors from the crystallization of the first lot. The solution is boiled with a little Norite, filtered, and cooled to -10°. The crystals which form are collected on a filter, washed with 10 cc. of cold methyl alcohol, and dried. There is obtained 43-48 g. of pale straw-colored material, m. p. 87-89°. The product is recrystallized from 25 cc. of pure methyl alcohol and washed with 10 cc. of cold methyl alcohol; there is obtained 37-41 g., m. p. 88.5-89.5°, making a total yield of material of this purity of 210-232 g. (66-73 per cent of the theoretical amount) (Notes 6 and 7).

2. Notes

1. The absolute alcohol may be prepared by drying 95 per cent alcohol twice with lime, or once with lime and once with sodium according to Note 1, Org. Syn. Coll. Vol. 1, 246, or commercial absolute alcohol may be dried once with lime or sodium just before use.

2. Benzyl cyanide was prepared according to Org. Syn. Coll. Vol. 1, 101, and purified according to Org. Syn. 16, 89.

3. Commercial absolute ethyl acetate was refluxed for one-half hour over phosphorus pentoxide and distilled just before use.

4. If time permits, the procedure may be continued without allowing the mixture to stand overnight. If the drying of the alcohol and ethyl acetate is begun in the morning, however, this is a convenient point at which to interrupt the procedure.

5. If used for the preparation of methyl benzyl ketone (p. 54) the product should not be dried.

6. It does not pay to attempt to recover more pure material by concentration of the mother liquors.

7. The number of steps may be decreased by omitting the isolation of the sodium salt. If this procedure is followed, the reaction mixture, after standing overnight, is diluted in a 5-l. flask with 2 l. of water and shaken until the sodium salt dissolves. A liter of cracked ice is added and the mixture extracted with one 1-l. and two 500-cc. portions of ether. The extracted aqueous solution is freed of ether as above and precipitated with a solution of 150 cc. of glacial acetic acid in 400 cc. of water, filtered, and washed with water. The product is colored and of lower melting point than that obtained from the purified sodium salt, and must be recrystallized twice from methyl alcohol to reach a melting point of 88.5–89.5°. The total yield of material of this melting point is somewhat less than that given above.

3. Methods of Preparation

α -Phenylacetoacetonitrile has been prepared by the condensation of ethyl acetate with the sodium derivative of benzyl

cyanide prepared from benzyl cyanide and sodium amide in ether,¹ and by condensation of ethyl acetate and benzyl cyanide by means of dry ² or alcoholic ³ sodium ethylate.

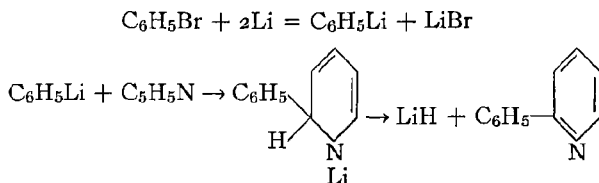
¹ Bodroux, Compt. rend. **151**, 234 (1910); Bull. soc. chim. (4) **7**, 848 (1910).

² Walther and Schickler, J. prakt. Chem. (2) **55**, 305 (1897).

³ Beckh, Ber. **31**, 3160 (1898); Post and Michalek, J. Am. Chem. Soc. **52**, 4358 (1930)

XXV

2-PHENYLPYRIDINE



Submitted by J. C. W. EVANS and C. F. H. ALLEN.

Checked by REYNOLD C. FUSON, W. E. ROSS, and E. A. CLEVELAND.

1. Procedure

IN a 1-l. three-necked flask fitted with a dropping funnel, a thermometer, mechanical stirrer, and reflux condenser protected from moisture (Note 1), the whole being swept with dry nitrogen, are placed 3.5 g. (0.5 gram atom) of lithium, cut into pieces the size of a pea, and 100 cc. of dry ether. The stirrer is started, and about 10 cc. of a mixture of 40 g. of bromobenzene (0.25 mole) in 50 cc. of dry ether is admitted from the dropping funnel; a vigorous reaction usually takes place (Note 2). The remainder of the mixture is added gradually over a half-hour period, when the metal should have largely disappeared (Note 3).

From the dropping funnel is next slowly introduced, with stirring, 40 g. (0.5 mole) of dry pyridine (Note 4) in 100 cc. of dry toluene. The ether is then distilled (Note 5) and the residual suspension stirred at 110° (inside temperature) for eight hours. It is then cooled to about 40°, 35 cc. of water cautiously added, and the liquids filtered if necessary (Note 6). The lower layer is separated and discarded. The toluene layer is dried for an hour with 20 g. of pulverized potassium hydroxide, and carefully distilled, using a fractionating flask (Org. Syn. Coll.

Vol. 1, 125). The low-boiling fraction (up to 150° at 760 mm.) is removed at ordinary pressure and the residue distilled *in vacuo*; after two fractional distillations, the yield of 2-phenylpyridine, b. p. 140° at 12 mm., is 15.5–19 g. (40–50 per cent of the theoretical amount).

2. Notes

1. The apparatus and reagents must be dried as for the Grignard reaction.

2. Occasionally the reaction will not start without the application of heat; as soon as the reaction begins, however, the source of heat is removed.

3. The yield of phenyllithium is approximately 75 per cent. It can be determined by allowing the phenyllithium to react with an excess of benzophenone and weighing the triphenylcarbinol formed. It is assumed that the carbinol is formed quantitatively.¹

4. The success of the preparation depends on the dryness of the pyridine. The pyridine was refluxed for eight hours over fresh quicklime and distilled, and then a similar treatment with pulverized potassium hydroxide followed. None of the available barium oxide gave as good results. Merck's medicinal pyridine gave the highest yields.

5. This is easily accomplished by running the water out of the condenser, while heating to 110°.

6. The small particles of unused metal that usually remain hinder the separation into layers.

3. Methods of Preparation

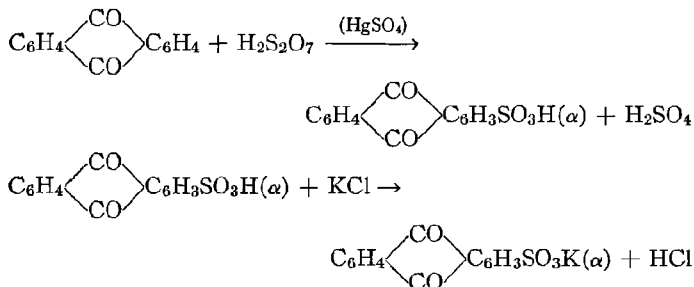
2-Phenylpyridine has been prepared in quantity only by heating phenyllithium with pyridine.² The use of a sealed tube is avoided by replacing the ether with toluene.³

¹ Gilman, Zoellner, and Selby, J. Am. Chem. Soc. 54, 1957 (1932).

² Ziegler and Zeiser, Ber. 63, 1847 (1930).

³ Walters and McElvain, J. Am. Chem. Soc. 55, 4625 (1933).

XXVI

POTASSIUM ANTHRAQUINONE- α -SULFONATE

Submitted by W. J. SCOTT and C. F. H. ALLEN.

Checked by L. F. FIESER and E. B. HERSHBERG.

1. Procedure

A 500-cc. three-necked flask fitted with a mechanical stirrer (Note 1) and a thermometer is half immersed in an oil bath mounted in a hood. In the flask are placed 120 g. of 19-22 per cent oleum and 1 g. of yellow mercuric oxide, the bath is warmed to 100°, and 100 g. (0.48 mole) of anthraquinone (Note 2) is added through a powder funnel attached by a piece of wide rubber tubing. The mixture is stirred vigorously and heated at 147-152° for forty-five to sixty minutes, after which the bath is removed and the flask is lowered from the stirrer and replaced by a 2-l. beaker containing 1 l. of hot water. While the water is being stirred, the hot acid solution is poured cautiously down the inner wall of the beaker; the mixture is then boiled for five minutes longer with stirring. After the unchanged anthraquinone (53-59 g.) (Note 3) is collected by suction on a 20-cm. Buchner funnel provided with a cotton filter cloth, it is washed with 200

cc. of hot water. The light brown filtrate, together with the wash water, is heated to 90° , and a solution of 32 g. of potassium chloride in 250 cc. of water is added. After cooling to room temperature (Note 4), the potassium salt, which crystallizes in the form of pale yellow leaflets, is collected on a large Buchner funnel (filter paper) and washed with 200 cc. of cold water. The yield of product, dried at 100° *in vacuo*, is 57–55 g. (Note 5) (77–86 per cent of the theoretical amount based on the anthraquinone converted) (Notes 6 and 7).

2. Notes

1. It is necessary to provide an efficient stirrer driven by a powerful motor. The yields reported were obtained using a Hershberg Chromel wire stirrer (Org. Syn. 17, 31); with other stirrers the yields were lower by about 10 per cent.

2. The anthraquinone employed melted at $284.5\text{--}285.5^{\circ}$ (corr.). It may be prepared conveniently by oxidation of anthracene (Org. Syn. 16, 74).

3. The recovered material contains mercury and other impurities and melts at $265\text{--}275^{\circ}$. When this is used as such in a second run, there is considerably more disulfonation than with pure anthraquinone.

4. Under the conditions specified very little disulfonation occurs, so that the crystallizing mixture may be allowed to cool to 25° without danger of contamination of the product with disulfonates. When recovered anthraquinone is employed, it is advisable to collect the product when the mixture has cooled to 60° , for the disulfonates present in this case are then retained in the mother liquor. The solubility of the 1,5- and 1,8-disulfonates increases more rapidly with increasing temperature than that of the α -monosulfonate.

5. The 57-g. yield refers to the experiment in which 53 g. of starting material was recovered; the percentage yield improves with increase in the amount of anthraquinone recovered.

6. The purity of the product may be checked by converting a sample to α -chloroanthraquinone (p. 15) and taking the

melting point; that from the above salt melted at 158–160° (corr.).

7. The conditions adopted in this procedure favor the production of α -monosulfonate in a state of high purity at the expense of a high conversion of anthraquinone. A better conversion can be achieved by conducting the sulfonation at a higher temperature, or by using more oleum, but in either case there is a considerable increase in the amount of disulfonic acids formed. The extent of β -sulfonation is not influenced greatly by the temperature, but is dependent chiefly on the amount of mercuric salt present in the solution. The amount specified corresponds approximately to the limit of solubility of the salt in the acid employed, and very little of the β -acid is formed. As the potassium β -sulfonate is more soluble than the α -salt, traces of this isomer are easily eliminated by crystallization.

3. Methods of Preparation

The only practical method for the preparation of anthraquinone- α -sulfonates is that based upon the discovery¹ that in the presence of a small amount of mercuric salt anthraquinone is sulfonated chiefly in the α - rather than in the β -position. Detailed procedures are described by Fierz-David,² by Lauer,³ and by Groggins;⁴ the above directions are based largely upon the observations of Lauer.³

¹ Iljinsky, Ber. **36**, 4194 (1903); R. E. Schmidt, *ibid.* **37**, 66 (1904).

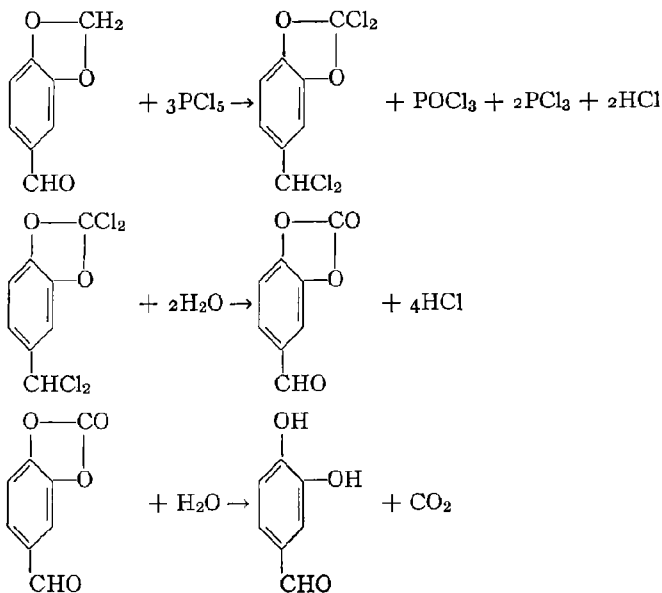
² Fierz-David, Helv. Chim. Acta **10**, 197 (1927).

³ Lauer, J. prakt. Chem. (2) **130**, 185 (1931); *ibid.* (2) **135**, 164 (1932).

⁴ Groggins, "Unit Processes in Organic Synthesis," pp. 268–269, McGraw-Hill Book Company, New York, 1935.

XXVII

PROTocatechualdehyde



Submitted by JOHANNES S. BUCK and F. J. ZIMMERMANN.

Checked by REYNOLD C. FUSON and W. E. ROSS.

1. Procedure

To 108 g. (0.72 mole) of piperonal in a 3-l. round-bottomed flask is added, in portions of 20 to 30 g., 454 g. (2.18 moles) of fresh phosphorus pentachloride. The flask is kept cold with ice to control the vigorous reaction, and care is taken to exclude moisture. After about half of the pentachloride has been added the reaction becomes sluggish and cooling is unnecessary

during the remainder of the addition. The entire process of addition requires about thirty minutes. The resulting green or blue liquid containing undissolved pentachloride is heated very gently over a flame for about sixty minutes to expel hydrogen chloride. From the turbid, light brown liquid thus formed, volatile material is removed under reduced pressure (water pump) on a steam bath. This operation takes about thirty minutes. The contents of the flask is then poured into 5 l. of cold water contained in a 12-l. round-bottomed flask (Note). A milky oil is formed which rises and sinks in the water and, after about thirty minutes, becomes solid. After standing overnight, the mixture is boiled gently for three hours. The brown solution, containing a little tar, is cleared with charcoal and evaporated under reduced pressure to about 700 cc., when the aldehyde begins to separate. The solution is allowed to stand overnight in the cold (about 0°); a large crop of crystals separates, is collected on a filter, and washed with a little water. The product is purified by recrystallization from three times its weight of water. It melts at 153–154°, with decomposition. The yield is 61 g. (62 per cent of the theoretical amount).

2. Note

This must be done cautiously because the residual phosphorus pentachloride reacts vigorously with water.

3. Other Methods of Preparation

Protocatechualdehyde has been made by a variety of methods, but is usually prepared from catechol by the Reimer-Tiemann method;¹ by demethylation of vanillin,² or veratric aldehyde;³ or from piperonal by the action of phosphorus pentachloride followed by hydrolysis.⁴

¹ Reimer and Tiemann, *Ber.* **9**, 1268 (1876); Tiemann and Koppe, *ibid.* **14**, 2015 (1881).

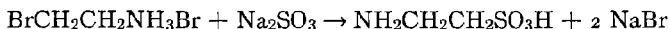
² Tiemann and Haarmann, *ibid.* **7**, 608 (1874).

³ Dreyfus, *Ger. pat.* 193,958 [*Chem. Zentr.* **I**, 1112 (1908)].

⁴ Fittig and Remsen, *Ann.* **159**, 129 (1871); Pauly, *Ber.* **40**, 3096 (1907); Barger, *J. Chem. Soc.* **93**, 563 (1908); Hoering and Baum, *Ber.* **41**, 1914 (1908).

XXVIII

TAURINE



Submitted by FRANK CORTESE.

Checked by C. S. MARVEL and C. L. FLEMING.

1. Procedure

A SOLUTION of 615 g. (3 moles) of β -bromoethylamine hydrobromide (p. 13) and 416 g. (3.3 moles) of anhydrous sodium sulfite (U. S. P.) (Note) in 2400 cc. of water is concentrated on the steam bath to a minimum volume (thirty-six to forty-eight hours). After the mixture has cooled, the cold moist cake is triturated with 1500 cc. of concentrated hydrochloric acid and collected on an asbestos mat in a Buchner funnel. The precipitate is washed ten times with 150-cc. portions of concentrated hydrochloric acid. The filtrate is mixed well, decanted from precipitated salts if necessary, and concentrated over a free flame to a volume of 600 cc.

Twenty-four hundred cubic centimeters of 95 per cent ethyl alcohol is added, with vigorous stirring, to the hot mixture. After fifteen minutes, the product is collected on a filter, washed with 95 per cent ethyl alcohol until it is colorless, and air-dried. The crude material is purified by dissolving it in four times its weight of hot water, adding decolorizing carbon (Norite), filtering, and adding to the hot filtrate five volumes of 95 per cent ethyl alcohol.

This product is practically pure taurine; it decomposes at $305\text{--}310^\circ$ (Maquenne block). The yield is 255–275 g. (68–73 per cent of the theoretical amount).

2. Note

An equivalent quantity (831 g.) of the more expensive crystalline variety may be used.

3. Methods of Preparation

To the methods reviewed in an earlier volume¹ may be added the preparation by the oxidation of cystamine² and by the decarboxylation of cysteic acid.³ The method given in the procedure has appeared recently in the literature.⁴

¹ *Org. Syn.* **10**, 58.

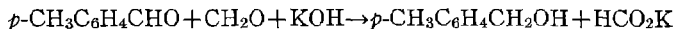
² Schoeberl, *Z. physiol. Chem.* **216**, 193 (1933).

³ Friedmann, *Beitr. chem. Physiol. Path.* **3**, 1 (1903); White and Fishman, *J. Biol. Chem.* **116**, 457 (1936).

⁴ Cortese, *J. Am. Chem. Soc.* **58**, 191 (1936).

XXIX

p-TOLYLCARBINOL



Submitted by DAVID DAVIDSON and MARVIN WEISS.

Checked by REYNOLD C. FUSON and E. A. CLEVELAND.

1. Procedure

THE apparatus consists of a 3-l. three-necked flask fitted with a mercury-sealed mechanical stirrer, a reflux condenser, a dropping funnel, and a thermometer which reaches almost to the bottom of the flask. Five hundred grams of potassium hydroxide pellets (85 per cent potassium hydroxide) (7.5 moles) and 750 cc. of commercial absolute methyl alcohol (free from acetone) are placed in the flask and stirring begun. The bulk of the alkali dissolves in a few minutes, with the evolution of heat. The flask is now surrounded by an ample cold-water bath, and, when the internal temperature drops to 60°, addition of a mixture of 360 g. (353 cc., 3 moles) of *p*-tolualdehyde (Note 1), 300 cc. of formalin (3.9 moles) (Note 2), and 300 cc. of absolute methyl alcohol is begun at such a rate that the internal temperature remains at 60–70°. This addition requires about fifteen minutes. The internal temperature is then maintained at 60–70° for three hours, after which the reflux condenser is replaced by a downward condenser, and the methyl alcohol distilled with the aid of a brine bath until the internal temperature reaches 101°. Nine hundred cubic centimeters of cold water is then added to the warm residue, and the mixture cooled. The resulting two layers are separated at once (Note 3), and the aqueous layer extracted with three 200-cc. portions of benzene. The combined oil and extracts are washed with five or six 50-cc. portions of water (Note 4), and the combined washings extracted

with 50 cc. of benzene, the benzene layer being added to the washed extract. The benzene solution is cleared by shaking it with a few grams of anhydrous sodium sulfate and is then distilled under diminished pressure. After removal of the benzene, 331 g. (90 per cent of the theoretical amount) of *p*-tolylcarbinol (b. p. 116-118°/20 mm.) is obtained; it solidifies in the receiver to a mass of oil-drenched crystals melting at 54-55°. Recrystallization from an equal weight of commercial heptane (b. p. 90-100°) gives an 80 per cent recovery of long needles which melt at 61°. A further 8 per cent is recoverable by concentration of the mother liquor (Notes 5 and 6).

2. Notes

1. A technical grade of *p*-tolualdehyde, obtained from Fritzsche Brothers, New York, New York, was found satisfactory.

2. The formaldehyde content of the solution is determined by analysis (cf. Org. Syn. 16, 82).

3. The upper layer solidifies if allowed to stand.

4. This washing removes potassium *p*-toluate, which causes difficulty in the distillation of the product if allowed to remain.

5. The final residue from the mother liquor is an oil which does not solidify in a freezing mixture, and appears to be a mixture of *p*- and *m*-tolylcarbinols. Only a trace of phthalic acid (phenolphthalein test) was obtained by oxidizing this oil with permanganate; the portion of it which was more readily soluble in water yielded a phenylurethan which depressed the melting point of the phenylurethan of either *p*-tolylcarbinol or benzyl alcohol.

6. Under the same conditions, benzaldehyde yielded 80 per cent of benzyl alcohol and piperonal 86 per cent of piperonyl alcohol.

3. Methods of Preparation

p-Tolylcarbinol has been prepared from *p*-tolualdehyde by the action of alcoholic potassium hydroxide,¹ by electrolytic

reduction,² and by the reducing action of the Grignard reagent,³ as well as from *p*-toluic acid by electrolytic reduction.⁴

The present procedure was adapted from a general method of preparing aromatic alcohols recently described.⁵

¹ Cannizzaro, Ann. **124**, 252 (1862).

² Law, J. Chem. Soc. **91**, 748 (1907).

³ Oddo, Gazz. chim. ital. **41**, I, 273 (1911).

⁴ Mettler, Ber. **39**, 2933 (1906).

⁵ Davidson and Bogert, J. Am. Chem. Soc. **57**, 905 (1935).

APPENDIX

LATER REFERENCES TO PREPARATIONS IN PRECEDING VOLUMES

(The following references are to methods of possible preparative value that have been described recently. The numbers in parentheses following the name of the compound refer to the volume and page of *Organic Syntheses*.)

Acetol (10, 1): By the action of buffered phosphate solutions on hexoses. Nodzu and Matsui, *Bull. Chem. Soc. Japan* **10**, 467 (1935) [*C. A.* **30**, 1748 (1936)].

Benzil (Coll. Vol. **1**, 80): By oxidation of desoxybenzoin with selenium dioxide in acetic anhydride at 140–150°, in 90 per cent yield. Hatt, Pilgrim, and Hurran, *J. Chem. Soc.* **1936**, 93.

Benzohydrol (Coll. Vol. **1**, 84): In 88 per cent yield from *N,N*-diphenylformamide and 3 moles of phenylmagnesium bromide. Maxim and Mavrodineanu, *Bull. soc. chim.* (5) **3**, 1084 (1936).

Benzoin (Coll. Vol. **1**, 88): From phenylglyoxal and benzene in the presence of aluminum chloride, in 90 per cent yield. Arnold and Fuson, *J. Am. Chem. Soc.* **58**, 1295 (1936).

To minimize the influence of inhibiting agents it is recommended that benzaldehyde for this preparation be allowed to stand overnight with 0.2 per cent of its weight of potassium cyanide, in an inert atmosphere. Ferreira and Wheeler, *Proc. Indian Acad. Sci.* **2A**, 605 (1935) [*C. A.* **30**, 2561 (1936)].

Benzophenone (Coll. Vol. **1**, 89): In 57 per cent yield from benzoyl chloride and diphenylcadmium or phenylcadmium halides, prepared by adding cadmium chloride to 2 moles of phenylmagnesium bromide. Gilman and Nelson, *Rec. trav. chim.* **55**, 518 (1936).

o-Bromophenol (14, 14): An improvement of the original method. Huston and Neeley, *J. Am. Chem. Soc.* **57**, 2176 (1935).

Catechol (Coll. Vol. **1**, 143): By the hydrolysis of *o*-chlorophenol in an aqueous solution of sodium and strontium hydroxides in the presence of copper or a copper compound. U. S. pat. 2,041,592 [*C. A.* **30**, 4513 (1936)].

p-Chlorobenzaldehyde (12, 12): In 77 per cent yield by warming *sym.*-*p*-chlorobenzoyl 2,5-dichlorobenzenesulfonylhydrazide with alkali. McFadyen and Stevens, *J. Chem. Soc.* **1936**, 584.

1,4-Dibenzoylbutane (13, 32): In 35 per cent yields from adiponitrile and phenylmagnesium bromide. Compère, *Bull. soc. chim. Belg.* **44**, 523 (1935).

β -Diethylaminoethyl Alcohol (14, 28): By the action of ethyl sulfate on ethanolamine at 200°. Fr. pat. 792,046 [*C. A.* **30**, 4176 (1936)].

1,4-Diphenylbutadiene (16, 28): In yields of 50 per cent by reduction of β -bromostyrene with hydrazine hydrate in the presence of a palladium catalyst and alco-

holic alkali at 140° and 10 atm. Busch and Weber, J. prakt. Chem. (2) 146, 54 (1936).

Diphenylmethane (14, 34): By adding formalin to a mixture of concentrated sulfuric acid, ethyl alcohol, and benzene. British pat. 446,450 [C. A. 30, 6760 (1935)].

Di-*p*-tolylmercury (Coll. Vol. 1, 226): In 93.5 per cent yields by refluxing an alcoholic suspension of *p*-tolylmercuric chloride with sodium carbonate and hydrazine hydrate. Gilman and Barnett, Rec. trav. chim. 55, 563 (1936).

Ethyl Acetoacetate (Coll. Vol. 1, 230): It is reported that, when the condensation is carried out in such a manner as to remove the alcohol formed in the reaction, the yield is 80 per cent of the theoretical amount. Roberts and McElvain, J. Am. Chem. Soc. 59, 2007 (1937).

Ethyl Phenylmalonate (16, 33): By condensing ethyl phenylacetate with ethyl carbonate using a sodium-potassium alloy. Skinner, J. Am. Chem. Soc. 59, 322 (1937); cf. Nelson and Cretcher, *ibid.* 50, 2758 (1928).

Furoic Acid (Coll. Vol. 1, 270): Furfural is oxidized with oxygen in the presence of an activator, consisting mainly of silver, in dilute sodium hydroxide solutions. U. S. pat. 2,041,184 [C. A. 30, 4515 (1936)].

***n*-Heptoic Acid** (16, 39): In 30 per cent yields by the action of sodium and carbon dioxide at 20 atm. on *n*-hexyl chloride in ligroin. Morton, LeFevre, and Hechenbleikner, J. Am. Chem. Soc. 58, 754 (1936).

Hydrogen Bromide (15, 35): In 80-90 per cent yields by the addition of bromine dropwise to petroleum in the presence of aluminum bromide. Ionescu and Radulescu, Bull. soc. chim. România 17, 309 (1935) [C. A. 30, 6300 (1936)].

Lauryl Alcohol (10, 62): By the reduction of ethyl laurate at 260° over a nickel catalyst. Pallray and Sabctay, Bull. soc. chim. (5) 3, 682 (1936).

***dl*-Methionine** (14, 58): A 78 per cent yield of ethyl α -benzamido- γ -chlorobutyrate is obtained by treatment of α -benzamido- γ -butyrolactone with absolute ethyl alcohol and hydrogen chloride. Subsequent action of sodium methyl mercaptide produces ethyl α -benzamido- γ -methylmercaptobutyrate, which by alkaline hydrolysis gives benzoylmethionine in a yield of 72 per cent, based on the chloro compound. Further hydrolysis with acid produces a 55 per cent yield of methionine. Hill and Robson, Biochem. J. 30, 248 (1936).

Methyl *iso*-Propyl Ketone (13, 68): In 80 per cent yields by hydrolysis of 2,3-dibromo-2-methylbutane with Twitchell's reagent. Colonge, Bull. soc. chim. (5) 3, 501 (1936).

Myristic Acid (Coll. Vol. 1, 371): An improved apparatus for fractionation of the methyl esters from coconut oil. Lepkovsky, Feskov, and Evans, J. Am. Chem. Soc. 58, 978 (1936).

2-Nitrofluorene (13, 74): In a yield of 70 per cent by passing nitrous vapors into a benzene solution of fluorene. Monti, Martello, and Valente, Gazz. chim. ital. 66, 31 (1936).

Phthalaldehyde Acid (16, 68): By chlorination of phthalide, followed by hydrolysis with boiling water and crystallization from benzene. Austin and Bousquet, U. S. pat. 2,047,946 [C. A. 30, 6011 (1936)].

In a 47 per cent yield from *o*-chlorobenzaldehyde, sodium, and carbon dioxide. Morton, LeFevre, and Hechenbleikner, J. Am. Chem. Soc. 58, 754 (1936).

Phthalide (16, 71): In a 90 per cent yield by electrolytic reduction of ammonium

phthalate in neutral or slightly acid solution using a pure lead cathode. Parodi Delfino and Somlo, IX Congr. intern. quim. pura aplicada **4**, 360 (1934) [C. A. **30**, 2855 (1936)].

o-Phthalyl Chloride (**11**, 88): In nearly quantitative yields by the interaction of phthalic anhydride and thionyl chloride at 220° in the presence of very small amounts of zinc chloride. Kyrides, J. Am. Chem. Soc. **59**, 206 (1937).

Piperonylic Acid (**10**, 82): By the oxidation of isosafrole with ozonized air. Ono and Imoto, J. Chem. Soc. Japan **57**, 701 (1936).

Propionaldehyde (**12**, 64): In a 70 per cent yield by passing steam and propylene oxide over silica gel at 300°. Ger. pat. 618,972 [C. A. **30**, 1066 (1936)].

Pyromellitic Acid (**10**, 90): By the oxidation of 5,6-tetrahydrobenzindane-1-one with nitric acid. Darzens and Lévy, Compt. rend. **201**, 902 (1935).

Quinone (**16**, 73): In nearly quantitative yields and of high purity by using potassium bromate as the oxidizing agent. McCoy, J. Chem. Education **14**, 494 (1937).

dl-Tartaric Acid (Coll. Vol. **1**, 484): By the oxidation of fumaric acid with hydrogen peroxide in *tert.*-butyl alcohol in the presence of osmium tetroxide. Milas and Sussman, J. Am. Chem. Soc. **58**, 1302 (1936).

Thiophene (**12**, 72): In a 31 per cent yield by passing furan and hydrogen sulfide over hot alumina. Yur'ev, Ber. **69**, 440 (1936).

l-Tryptophane (**10**, 100): By condensation of indole-3-aldehyde with hydantoin in the presence of piperidine, followed by treatment of the product with ammonium sulfide and ammonium hydroxide at 100° for 500 hours. Boyd and Robson, Biochem. J. **29**, 2256 (1935).

Xanthone (Coll. Vol. **1**, 537): In nearly quantitative yields by distillation *in vacuo* of the acid chloride formed by the action of thionyl chloride on the phenyl ether of salicylic acid. Lock and Kempter, Monatsh. **67**, 24 (1936).

ADDITIONS AND CORRECTIONS FOR PRECEDING VOLUMES

(The numbers in parentheses following the name of the compound refer to the volume and page of Organic Syntheses. New methods or changes in procedure have not been checked unless otherwise noted.)

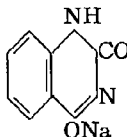
Benzohydrol (Coll. Vol. 1, 84):

A number of runs in which the brown color (see Note 2) was not observed were found to give quantitative yields. The sodium hydroxide was even added last without affecting the yield adversely.

W. E. BACHMANN and F. Y. WISELOGLE, private communication. Checked by REYNOLD C. FUSON and R. O. SAUER.

Benzoylene Urea (17, 16):

The sodium salt of benzoylene urea has the formula



The statement in Note 5 refers to this salt rather than to benzoylene urea itself. The name F. E. SHEIBLEY is misspelled.

1,1-Diphenylethylene (Coll. Vol. 1, 221):

A large amount of high-boiling solid material—presumably the intermediate alcohol—is obtained by the original procedure. If the crude product, remaining after the removal of the ether, is boiled for an hour with 100 cc. of 20 per cent sulfuric acid, the aqueous layer removed, and the oil distilled (without being washed) under reduced pressure, the yield of pure hydrocarbon equals that claimed.

C. R. NOLLER and L. J. LATAILLADE, private communication.

Methyl Iodide (13, 6o):

Excellent yields are obtained by treating methyl sulfate with potassium iodide, and no special apparatus is required.

A 3-l. flask is provided with a mechanical stirrer, separatory funnel, thermometer, and small fractionating column leading to an efficient condenser set downward for distillation. A solution of 800 g. (4.8 moles) of U. S. P. potassium iodide in 430 cc. of water is placed in the flask, 60 g. of calcium carbonate is added, and the mixture is heated to 60–65°, with stirring.

The temperature is maintained at 60–65°, and 630 g. (473 cc., 5 moles) of "practical" methyl sulfate (caution—poison) is added gradually from the separatory funnel at such a rate that the methyl iodide distils briskly. About two hours is required for the addition. The distillate is collected in a receiver chilled thoroughly in an ice bath.

After all the methyl sulfate has been added the temperature is raised to 65–70° for about forty minutes to complete distillation of the methyl iodide. The product is separated from a small amount of water, dried thoroughly over anhydrous calcium chloride, and decanted into a dry distilling flask. A few crystals of solid potassium iodide are added, and the material is distilled from a water bath. The yield of methyl iodide, b. p. 41–43°, is 615–640 g. (90–94 per cent of the theoretical amount). Similar yields are obtained with quantities up to ten times the amounts given.

W. W. HARTMAN, private communication. Checked by JOHN R. JOHNSON and H. J. PASSINO.

***m*-Nitrophenol (Coll. Vol. 1, 396):**

After the *m*-nitrophenol is distilled the flask should be allowed to cool before air is admitted. Otherwise the residue may decompose with explosive violence.

W. E. BACHMANN and B. W. ROTTSCHAEFER, private communication.

Trichloroethyl Alcohol (15, 8o)

The number of moles of aluminum ethoxide used is 0.46.

SUBJECT INDEX

(This Index Comprises Material from Volumes X to XVIII of this Series; for Previous Volumes see Collective Volume I.)

(Names in small capital letters refer to the titles of preparations which are given in full detail. A number in ordinary bold-face type denotes the volume. A number in bold-face italics refers to a page which gives preparative directions for a substance formed either as principal product or as a by-product, or to a product which has been prepared by a method analogous to the one given. Other numbers in ordinary type indicate pages on which a compound is mentioned incidentally or information is given concerning an item other than a compound.)

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